Coronary Circulation in Health and Disease

BY

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73 Illustrations



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To My Wife

PREFACE

Diseases of the heart and especially of the coronary circulation have attained large proportions and constitute our most important economic and medical problem today. Despite this no adequate and critical summary of the investigative work directed at this problem exists. The purpose of this monograph is to consider some of the many advances that have resulted from various investigations and to attempt to crystallize our thinking regarding this the most important vascular bed in the body.

Following a general statement of the problem the morphological aspects of the coronary circulation are first considered. The main presentation is developed from the author's own experimental work which has extended over the past fifteen years. The development of experimental approaches to the study of the coronary circulation is considered extensively including the preparations used, the methods for determination and registration of mean and phasic cardiac pressures, coronary blood flow, coronary flow determinants and the metabolism and work of the heart. The experimental findings stress the peculiarities of the coronary circulation, the functioning of the distribution channels for coronary inflow and especially outflow, the interpretation of phasic flow and pressure curves, the determination and evaluation of the basic flow controlling mechanisms, the intimate action of drugs, the blood flow, metabolism and work of the myocardium and the physiological responses of the coronary circulation. The presentation is concluded with a consideration of heart disease and especially atherosclerosis in man. The attempts to create and study this condition through the experimental production in animals of coronary artery constriction or occlusion, cardiac hypertrophy and chronic congestive heart failure together with the associated compensatory physiological reactions are considered in some detail. It is pointed out that chronic congestive heart failure has not yet been produced experimentally. It is hoped that critical thinking about the known facts of the coronary circulation will open the door for the experimental production

of standardizable chronic heart failure in a proper experimental animal and thus, ultimately means to prevent or to correct it will be evolved

My excuse for all this is that I have been inveigled into it by the urging of well meaning friends I realize that it is but a very dim and sputtering candle among the bright lights of cardiac research still its writing has helped to orient my own thinking perhaps its reading will be of some small aid to others

I wish to thank numerous friends and colleagues who have encouraged me and made suggestions for improvements especially Dr C J Wiggers and Captain R D Seely M C who were kind enough to review the manuscript critically For many of the excellent drawings and photographs I am deeply indebted respectively to Mr C D Purpura and Mr A W Carpenter The criticisms of Lieutenant F H Longino, M C and the editorial and secretarial assistance of Miss Brunette Arnold are gratefully acknowledged

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FOREWORD

It must have been obvious to the ancients that some provident mechanism exists by which the coronary blood flow is adapted to the greatly varying needs of the heart both in health and disease. However, nature has zealously guarded the secrets of its regulation through a complexity of mechanisms, each of which can modify blood flow. In no field of the circulation have our viewpoints changed more frequently than in the interpretation of the coronary circulation. Experiments which in one epoch appeared crucial have proved less convincing or fallacious as new obstacles to a real understanding have appeared in research after research.

It is a duty as well as a privilege for qualified investigators occasionally to summarize current trends in the form of a monograph so that workers in related fields may keep in touch with contemporary knowledge. In order to be of real value, such reviews require more than categorical statements of contradictory conclusions reached by different groups of investigators. It cannot be assumed that all conclusions have equal value. Results must be analyzed and fairly appraised in relation to the experimental procedures employed. Unless this is done we are apt to confuse what can occur with that which does occur in the normally beating heart.

It is obvious that such evaluation of current work can be undertaken only by an investigator who himself has participated actively in experimental work for many years and has thereby gained the ability of recognizing the pitfalls that beset workers in the field. Moreover it can be done only by an individual who by temperament and training has developed the capacity to analyze critically his own work as well as that of others. An intimate association with Dr. Donald E. Gregg and familiarity with his approaches, attacks and analyses of problems convince me that he possesses all of these qualifications.

It will be obvious to readers that Dr. Gregg has built his interpretations essentially around results obtained by use of adequate apparatus and techniques on normally beating hearts in the body

He recognizes that a study of the coronary circulation requires a synthetic as well as an analytic approach, and that many special types of heart preparations were required as stepping stones toward a full understanding of the separate factors that control coronary flow However, his own interest and that of his numerous associates have chiefly been directed toward the integration of these factors in the normally beating heart under diverse experimental conditions If any criticism can be offered, it is that he has sometimes leaned too conservatively toward the side of caution When doubt exists as to interpretations of his own work or that of others he has frankly left an opinion pending But how much better than to err by speculating and theorizing on insecure or probable evidence!

Dr Gregg's thinking over many years as reflected in this monograph, has always been to correlate laboratory findings with physiological and clinical problems After analyzing the ways in which the coronary circulation adapts itself to the activities and vicissitudes of the healthy individual he has conservatively extended the application of current knowledge to various cardiac conditions found in disease

It may confidently be predicted that cardiovascular investigators cardiologists and progressive practitioners of general medicine will all feel that Dr Gregg has rendered a real service in launching this monograph *The Coronary Circulation in Health and Disease*

CARL J WIGGERS

CONTENTS

Coronary Circulation in Health and Disease

Chapter 1

INTRODUCTION A STATEMENT OF THE PROBLEM

DISEASE of the coronary architecture has long been recognized and the development of our knowledge of its importance in relation to heart disease has been traced by Willius and Dry[35] The clinical syndrome of angina pectoris was well described in England in 1768 by Heberden[14] and its association with changes in the coronary arteries was early observed by Fothergill[11] in 1776 and somewhat later by Hunter and others Probably the first case of coronary occlusion correctly diagnosed during life and confirmed at autopsy was by Hammer[14] in 1878 In 1910 Osler[25] observed that advanced coronary artery disease may be present at autopsy without much disturbance of cardiac activity and that in some fatal cases of angina pectoris very little disease of the heart or its blood vessels could be found It was not until 1912 that Herrick[17] gave a complete clinical discourse on sudden coronary occlusion and showed that patients may at times survive complete closure of a coronary artery The introduction of electrocardiography in 1903 by Einthoven[8] stimulated cardiac research [1] and the subsequent recognition of its value as a diagnostic tool so advanced our knowledge that the diagnosis of coronary artery disease can be readily made

As a prelude to a consideration of our knowledge of the functioning of the coronary circulation it is fitting that brief attention be given to the prevalence of the problem of disease of this system and the heart Accurate information concerning the present and past status of heart disease is not available anywhere in the world despite the long history of knowledge of its existence and despite the accumulation of much knowledge on the subject from various sources This is so in part because in such an approach to an evaluation of the problem any interpretation must be tempered by the realization that the data may be influenced by associated and uncontrollable factors such as (*1*) changes in classification and reporting procedures (most extensive in cardiovascular renal disease) (*2*) the ques

tionable accuracy of death certificates (3) changing emphasis or fashion in diagnoses (4) known reduction in incidence of other diseases which causes a corresponding increase in the ratio of deaths from heart disease, (5) aging of the population which accentuates heart disease because heart disease is more prevalent in the older age group, (6) incorrect sampling of the population for economic reasons or because of a lack of correlation of organic heart disease with the subjective symptoms Therefore, in the present state of knowledge, it is extremely hazardous to be dogmatic about the incidence, mortality trend, and etiological factors involved in heart disease It is much safer to consider the broad group of diseases of the cardiovascular system which includes the heart kidney, and intracranial lesions of vascular origin and possibly an ill defined cause senility which has concealed a large group of deaths from heart disease However, some rather general deductions can be made without much fear of contradiction From these, it is inescapably clear that heart disease constitutes our most important medical and public health problem today

It is estimated that 4 to 8 million persons in the United States are afflicted with some form of heart disease [31] The annual number of deaths 460 580 in 1947, is not only a staggering figure but is considerably more than twice the mortality from the second most frequent cause of death cancer, with 189 811 deaths in 1947 The figure for heart disease comprises about a third of deaths from all causes and approximates the next three leading causes combined (Table 1)

The situation is definitely not static The gain in crude death rates ascribed to heart disease and to all forms of cardiovascular renal disease has been considerable increasing from 420 per 100 000

TABLE 1 —COMPARATIVE RANK OF MAJOR CAUSES OF DEATH 1947 *

		Total Deaths	Rate per 100 000 Population
1	Diseases of heart (all forms)	460 580	3[illegible]1 [illegible]
2	Cancer and other malignant tumors	189 811	132 4
3	Intracranial lesions of vascular origin	131 039	91 4
4	Accidents (all forms)	124 942	86 3
5	Nephritis	80 [illegible]88	56 0
6	Congenital malformations and diseases of first year of life (including premature births)	81 [illegible]	53 [illegible]
7	Pneumonia (all forms) and influenza	61,836	43 1
8	Tuberculosis (all forms)	48 064	33 5

population in 1930 to 520 per 100 000 population in 1945 with all of the increase assigned to heart disease[34] (See Fig 1) The most striking increase in the crude death rate is from heart disease in the older age group including coronary artery disease hypertension and other types of non valvular heart disease In the individual age groups from thirty five to eighty five years broken down into ten year periods the crude mortality assigned to heart disease has increased for each age group over forty five years of age and has declined in all the younger age groups the general decline arising chiefly from a fall in the incidence of rheumatic heart disease[36] (Fig 2)

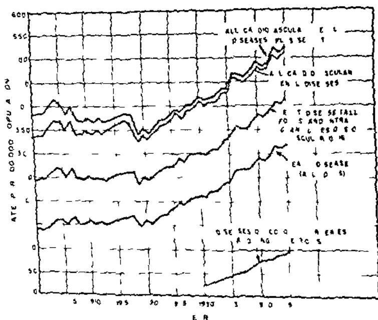


FIG 1 *Cumulative* crude death rates for all *forms* of heart disease cardiovascular renal diseases and senility Death registration States (1900-1945) (*Wooley and Mortimer*[34])

Such crude death rates showing the proportion of the population lost each year *are a valid* measure of the impact of this disease Therefore it is not *surprising that the* outlook for the older patient with heart disease *is regarded* as poor and that the situation is believed out of hand One obvious *explanation* is the increase in total population and the lengthened *span of life in the* older age group (from better control of infectious diseases) so that there is now a much larger proportion of the total population over forty to forty

five years of age, an age period in which hypertension and arteriosclerotic heart disease are more likely to occur For example in 1930 the life span approximated fifty seven years in 1944 it approximated sixty four years When the death rates are corrected for aging of the population the deaths in all age groups for all cardiovascular-renal diseases show a slight downward trend and deaths

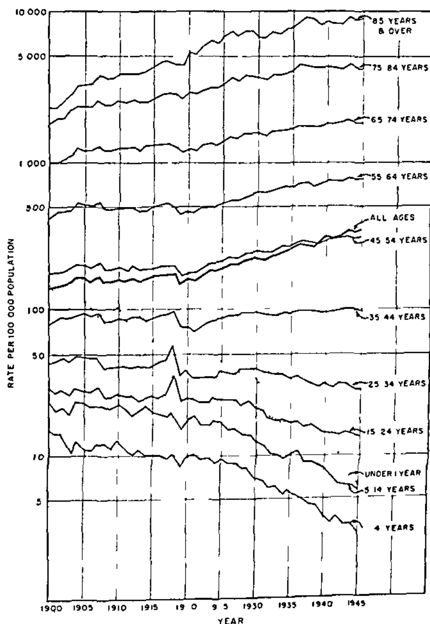


Fig 2 —Age specific death rates for all forms of heart disease (on logarithmic scale) Death registration States (1900–1945) (Woolsey and Moriyama[36])

due to heart disease have increased only slightly during this period[38] (Fig 3) Even this small increase may be more apparent than real for it is believed explainable by the shifting pattern in diagnosis which now emphasizes cardiac disease rather than nephritis and cerebral hemorrhage

In any evaluation of the status of heart disease it is essential to consider the ways in which the heart can fail Cardiac failure can arise from infections such as rheumatic fever bacterial endocarditis syphilis or may be associated with non infectious states such as coronary arteriosclerosis systemic hypertension with or without associated coronary arteriosclerosis pulmonary hypertension and

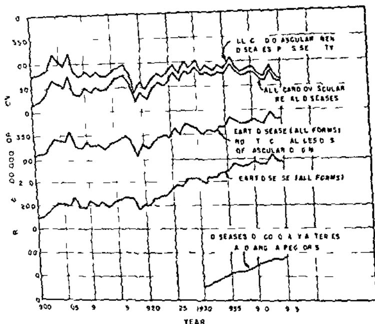


FIG 3 – Cumulative age-adjusted death rates (adjusted by the direct method) for all forms of heart disease cardiovascular renal diseases and senility Death registration States (1900–1945) (Woolsey and Moriyama[36])

thyroid disease Irrespective of the clinical condition the incidence of and mortality from heart disease must be based ultimately on one of two states either insufficiency of the coronary circulation or disease of the myocardium In absolute coronary insufficiency a coronary artery or a branch is closed or its lumen is decreased thus causing the heart either to be hypodynamic or to fibrillate Such stenosis and/or closure arises from arteriosclerosis from thrombosis on an arteriosclerotic basis from intramural hemorrhage or on a

five years of age, an age period in which hypertension and arterio-sclerotic heart disease are more likely to occur. For example in 1930 the life span approximated fifty-seven years, in 1944 it approximated sixty-four years. When the death rates are corrected for aging of the population, the deaths in all age groups for all cardio-vascular renal diseases show a slight downward trend and deaths

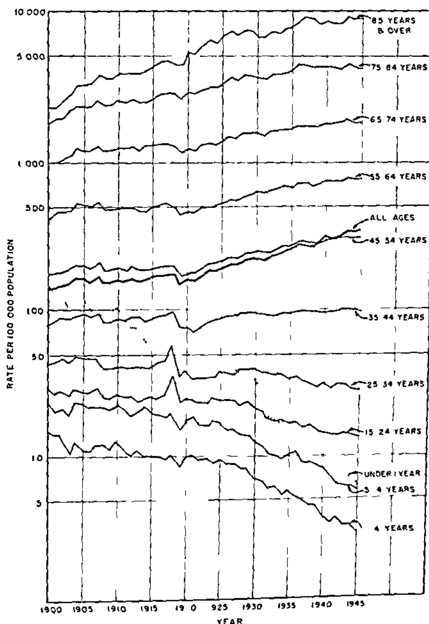


Fig 2.—Age specific death rate for all forms of heart disease (on logarithmic scale) Death registration States (1900–1945) (Woolsey and Moriyama [36])

tent of coronary arteriosclerosis but the state of nutrition fluctuates greatly during the average life and the state found at death may be entirely different from that existing during life In support of this view may be advanced (*1*) in a statistical analysis of *200 000 men* the death rate from coronary arteriosclerosis in overweight men was at least twice that in normal weight men [8] (*2*) in unselected consecutive *autopsies of individuals over the age of thirty years* the incidence of advanced coronary arteriosclerosis was much greater in obese individuals and was *independent* of age sex increased blood pressure heart weight and diabetes [14] and in eighty consecutive cases of fatal coronary arteriosclerosis in young *soldiers* 91 per cent were overweight [15] (*3*) in parts of the world where poor nutrition is prevalent a low incidence of coronary arteriosclerosis is reported especially in China and Costa Rica [17, 9] However despite the preceding it cannot be denied that obesity is more prevalent in women than in men and yet clinical or *necropsy* evidence of arteriosclerosis in the coronary arteries is far less common in women

The various views expressed concerning the incidence of coronary artery disease in relation to different occupations have been conflicting By some the opinion is held that professional men such as physicians lawyers and business executives are more vulnerable to coronary disease than are laborers and farmers and this possibly because of sustained mental alertness work anxiety irregularity of rest food and exercise In line with this idea the recorded coronary death rate of male physicians has been reported as approximately twice that of white males of the same ages in the general population [19] However others could find *no greater incidence of* coronary artery disease among physicians and professional men than *in the general population* [10-3]

Heredity is accepted by many students as a significant etiological factor in coronary artery disease In congenital xanthomatosis coronary occlusion is almost inevitable and often is manifest in the twenties or even earlier [9] The fact that the intima of the coronary arteries lying in the epicardium (to which region coronary arteriosclerosis is largely restricted) is much thicker in the male than in the female from birth on [12] may establish the basis for the sex *difference* in the incidence of coronary arteriosclerosis

The frequency of the association of arteriosclerosis in the systemic and coronary arteries in older patients with diabetes is almost unequaled by that of any other disease The incidence of coronary artery disease in diabetic persons has been investigated repeatedly at autopsy with general agreement that severe or significant arteriosclerosis is more frequent in diabetics than in non-diabetics Over

non arteriosclerotic basis, from embolism inflammation and syphilis. Hearts with relative coronary insufficiency may also fail because presumably abnormally high work demands are made as in congenital hearts in essential hypertension and as the result of valvular lesions from infectious processes. In disease of the myocardium, the heart fails because the muscle is damaged by an infectious agent and thus has a relative incapacity for work, as in the acute stages of rheumatic fever.

With this in mind our present information is instructive. Although it is difficult to estimate the true distribution of heart disease between the coronary architecture and the myocardium the percentage of individuals with heart disease who have significant coronary artery disease (according to the clinical diagnosis) approximates 26 to 37 per cent.[1,20,3] In addition, necropsy sources indicate that 32 to 54 per cent of persons with organic heart disease die from diseases of the coronary arteries.[1,5,34] About a third die from myocardial failure associated with cardiac hypertrophy in cases of healed rheumatic valvular disease and hypertension without arteriosclerosis,[1] presumably on the basis of relative coronary insufficiency. The remainder approximately a third die of myocardial failure associated with some form of myocarditis.[1]

Heart disease in infants is quite rare and generally on a congenital basis. With age the mortality rises progressively and the rate of increase is especially rapid above the ages forty to forty five when it approximately doubles every ten years to reach its highest rate at the ages eighty to ninety.[36] However the predominant type of heart disease varies with the age. Rheumatic fever is the leading cause up to forty years, hypertension is relatively most important from forty to fifty years. In still older people the predominant cause is coronary arteriosclerosis with or without an associated hypertension.[33]

Heart disease and the mortality therefrom are much more prevalent *in males than in females*. This does not apply in children and younger adults in whom almost all cases are of rheumatic origin but in the older age group heart disease is far more frequent in males than in females presumably because of the much greater incidence of coronary artery disease in men than in women.[1,16,4,31,34]

Attention has been directed toward the relation of coronary heart disease to associated states with the hope that the etiology would be determined. This is the major problem in heart disease.

It is not generally accepted that a relationship exists between the state of *nutrition* and *coronary arteriosclerosis*. Establishment of such a relationship is particularly difficult because post mortem examination is the only satisfactory method of determining the ex

Approximately one-third of persons with heart disease ultimately die from primary myocardial failure one-third from primary coronary insufficiency associated with cardiac hypertrophy and increased work arising from valvular lesions and hypertension and the remaining one-third from primary coronary insufficiency on an arteriosclerotic basis Over nutrition and hypertension in the male sex of advanced age are associated with a high incidence of coronary arteriosclerosis the main lesion of the coronary arteries However, presumably no one factor can be considered responsible for the development of coronary arteriosclerosis for it can occur in the very young of either sex at any age without obesity and at a normal blood pressure At all events this brief recapitulation of the problem indicates that more attention should be centered on the coronary circulation since at least two-thirds of all heart disease and heart failure arises from a relative or absolute failure of this vascular tree

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the age of forty years functionally significant coronary arteriosclerosis occurred in 74 per cent of fifty diabetics and in 37 per cent of 400 controls The relative immunity of non-diabetic women to severe coronary arterial lesions was striking although male and female diabetic patients were equally affected [30] The incidence of such lesions in youthful patients is only beginning to be appreciated There is clinical evidence of premature arteriopathy in youthful diabetics after fifteen or more years of the disease A nutritional factor may also contribute to development of this disease *in youth as lesions are believed by some to be found only in* those individuals uncontrolled by diet and insulin over a period of years

Elevation of blood pressure is the most common associated finding in heart disease and heart failure The latter could arise from the excessive work thrown on the heart by the hypertension which leads to hypertrophy and failure However, the evidence is conflicting as to whether there is an associated increase in coronary artery disease in these individuals There is no doubt that the percentage (25 to 40 per cent) of hypertensive patients with coronary artery disease is high, [4,5,19] and some necropsy studies indicate that the incidence of coronary arteriosclerosis is many times greater in the hypertensive group (or those with heavy hearts with non valvular disease) *as compared to a corresponding group without hypertension* [4,6,34] However in 1000 autopsies, ages fifteen to ninety four of persons with blood pressure greater than 160/90 and without cardiac valve lesions, the incidence of coronary arteriosclerosis was no greater than in a similar group with a normal blood pressure [18]

Coincident with increased blood pressure or with long sustained valvular lesions the heart hypertrophies These heavy hearts are regarded by some to have a greater incidence and extent of coronary arteriosclerosis than do other hearts of a normal size [3,13]

In summary then perhaps the most significant fact concerning heart disease is the close relationship between the growing incidence of such disease and the aging of the population In the older age group, hypertension and arteriosclerosis are the most common causes *but in the younger age group there has been a sharp reduction* in the prevalence and mortality of heart disease because of the decline in rheumatic fever and better control of infectious diseases The over all rise in cardiac cases and death is the consequence of a successful effort to lengthen life chiefly through the reduction of the acute infections and it is the steady upward movement of the cardiac death rate in the 27 per cent of individuals who are forty five years of age or over that is largely responsible for the increase in rate at all ages

Chapter 2

GENERAL ANATOMIC CONSIDERATIONS

Myocardium.—The ventricular walls are made up of four discrete muscle bands or layers arising from fibrous structures at the base of the heart. Throughout much and possibly most of their course the different muscle bundles are separated by connective tissue which also contains blood vessels, nerves, and Purkinje-like cells.[16] The different muscle bundles are illustrated schematically in figure 4. The two superficial muscles, the sinospiral and bulbospiral, cover very thinly almost the entire surface of both ventricles to a depth of about a millimeter. These two muscle bands arise respectively from the right and left bases of the heart, course diagonally around the surfaces of both ventricles to converge at the apex where they penetrate to the interior of both ventricles to lie subendocardially and to run spirally upward, completely lining both ventricular cavities. In addition, some fibers extend further toward the interior of the ventricular cavities to form the papillary muscles from which fibrous tendons (*chordæ tendonæ*) attach to the valve leaflets (auriculo-ventricular valves). Other fibers from the superficial bulbospiral muscle constitute the lower portion of the septum. These two muscles presumably cause fixation of the A-V valve leaflets during systole, preventing regurgitation, and also may possibly fix the fulcrums so that the septum and the weak-walled apices do not bulge during systole.

The main muscular portion of both ventricles is made up of the two deep muscle bands, the sinospiral and bulbospiral, which arise from the mitral ring. The deep sinospiral is a powerful transverse constrictor (deficient at base and apex) which encircles both ventricles and forms most of the upper portion of the septum. The deep bulbospiral muscle is a heavy sphincter extending around the upper third of the left ventricle and surrounding the mitral and aortic orifices. It is probable that both muscles have a dominant function in emptying both ventricles and that, in addition, the deep bulbospiral is essential in maintaining aortic pressure toward the end of systole.

Conducting System.—In the auricles and ventricles of the human heart and mammals in general there are specialized muscle fibers (Purkinje cells) which are believed to subserve the function of conduction. As compared to ordinary cardiac muscle cells, they have a larger diameter, clearer cytoplasm, fewer cross striations, and possess

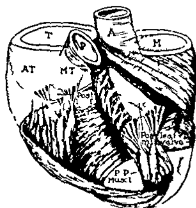
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peripheral myofibrillae[3,20,31,43,45] A collection of these cells the sino-atrial node lies in the sulcus terminalis another, the atrial ventricular node lies at the base of the interauricular septum just anterior to the mouth of the coronary sinus Several deep pathways containing specialized cells and unobstructed by connective tissue extend between the sino-atrial and atrial ventricular nodes The specialized cells are concentrated near the nodes and spread out to make end to-end transitions into the ordinary atrial muscle From the atrial ventricular node, parallel condensed strands of this tissue pass through the membranous septum as the bundle of His to divide into a broad flat sheet of fibers on the left and right to form the left and right bundle branches This specialized tissue is not merely a subendocardial layer but is a profuse myocardial network ramifying in many planes and extending nearly to the epicardium The two superficial muscles are innervated from their papillary ends by the anterior and posterior divisions of the left branch of the bundle of His The deep muscles are innervated by *penetrating branches* that emerge radially from the Purkinje system to the proper level and then turn to run parallel to the circular fibers This specialized tissue ends by a gradual end to-end transition into ordinary heart muscle The nodes the bundle its branches and the specialized tissue transitions into ordinary heart muscle are all *enclosed in a connective* tissue sheath[23]

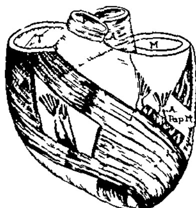
Recently the concept of the separation of cardiac muscle into discrete layers and the existence in the human and dog heart of such specialized muscle fibers has been challenged[5,9,13] However although no such system exists in poikilothermic vertebrates[5] its presence in the heart of the dog monkey and in the human fetus and embryo has been reaffirmed[23,24] Presumably, the negative findings arose from the use of gross dissection and inadequate staining technique

Sensory Innervation. – The mammalian heart is richly supplied with visceral afferent nerves

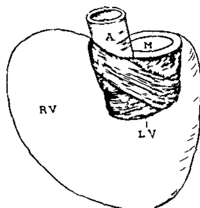
All of the non muscular tissues of the heart are richly supplied with myelinated *nerve fibers including* the pericardium epicardium endocardium interstitial *connective* tissue and valve structures[27,44] Since the structures innervated have no known motor function the fibers are presumably *sensory* *The coronary* arteries and their branches in the myocardium are especially heavily supplied with these myelinated fibers whose terminal divisions are filaments without myelin sheaths *some of* which presumably extend directly into the walls of the artery[18] Nerve endings in close relation to the myocardial muscle fibers and resembling receptors in skeletal muscle



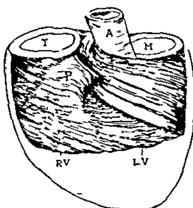
SUPERFICIAL BULBO SPIRAL



SUPERFICIAL SINO SPIRAL



DEEP BULBO SPIRAL



DEEP SINO SPIRAL

FIG 4 —*Upper Left* The superficial bulbospiral muscle as seen from the front of the heart A aorta M mitral orifice P pulmonary artery T tricuspid orifice AT, anterior leaflet of tricuspid valve MT medial leaflet of tricuspid valve Post leaf inferior (posterior) leaflet of the tricuspid valve PP inferior (posterior) leaflet of the mitral valve A v shaped section is cut from those fibers encircling the left ventricle subendocardially so that the mitral valve may be seen *Upper Right* The superficial sinospiral muscle as seen from the anterior surface of the heart Symbols as above *The subendocardial layer has been cut through in order to show deeper structures* The window in the right ventricular wall shows the fibers from the trabeculated area running up to the anterior and medial leaflets of the tricuspid valve *Lower Left* The deep bulbospiral muscle a powerful sphincter encircling the left ventricular base and enclosing both the aorta and the mitral orifice within its sweep Symbols as above *Lower Right* The deep sinospiral muscle as seen from the front Note the division of the muscle at the posterior interventricular sulcus with fibers passing anteriorly to form most of the basal two-thirds of the septum the septal fibers lie just distal to the band of the left head of origin at the base of the aorta Symbols as above (Robb and Robb[36])

DISTRIBUTION OF THE CORONARY VESSELS

1 Arteries —Two coronary arteries the right and left carry blood to the myocardium About 2 millimeters from its ostium the left coronary artery divides into the left circumflex and the anterior descending branches The former runs in the atrio-ventricular (A V) groove to the left ending in a posterior descending branch The anterior descending branch runs downward in the interventricular groove toward the apex Near its origin septal branches are given off The right coronary artery descends in the right (A V) sulcus and ends posteriorly as several descending branches over the right and left ventricles

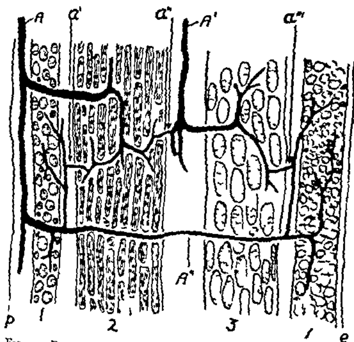


Fig 3 – Diagram illustrating the distribution of arteries among muscle layers of the myocardium P epicardium E endocardium 1 2 3 1 myocardial bundle A subepicardial branch A muscular branch A branch extending through thickness of wall A anastomotic channel (Lowe 23)

The subdivisions of the main coronary rami descend superficially in the general direction of the apex and give off myocardial branches which course directly into the ventricular muscle At or near the apex where the superficial muscle forms a spiral and penetrate to form the innermost (subendocardial) layer of muscle the terminal

have also been described, these consist of spirals encircling the muscle fibers of the myocardium and of endings similar to the neuromuscular spindle receptors of skeletal muscle.[18,30]

These visceral afferent (sensory) fibers in the nerves of the heart follow the myocardial and epicardial branches of the coronary arteries toward the base of the heart to form nerve trunks and are the *anatomical structures by which sensory nerve impulses are trans*mitted to the central nervous system. Degeneration studies following nerve section in cats show that the stellate and middle cervical *sympathetic ganglions, the thoracic dorsal roots* and the nodosa ganglions of the vagus nerves all supply afferent fibers to the subepicardial, subendocardial, and perivascular tissues of the myocardium.[27] *However, no conclusion is possible as to whether in the* human heart these afferent nerve fibers are part of the vagus nerve with their cell bodies in the nodosa ganglions or whether most of them accompany the sympathetic nerves and have their *cell* bodies in the dorsal root ganglions of the spinal cord as suggested by the known fact that stellate ganglionectomy relieves anginal pain. Their function is poorly understood, but no doubt at every systole and diastole the central nervous system normally receives volleys of impulses from various areas of the heart.

Autonomic Innervation.—The nerve supply to the *heart from the* autonomic nervous system is abundant although anatomical separation of the sympathetic and parasympathetic systems is somewhat difficult especially *in the heart, because of differential staining diffi*culties. Woollard[54] reported the presence of nerves, the terminal filaments of which pass among muscle fibers and within muscle cells. *Anatomical and physiological evidence indicates that cholinergic* (parasympathetic) fibers are distributed to the sino-atrial and atrial-ventricular nodes, to the main bundles and in some species, to the *proximal portions of the right and left branches to the myocardium* of the auricles and to the coronary arteries and that except for the guinea pig and frog ventricular muscle does not appear to be sup*plied by cholinergic fibers.*[7,8,37] *Adrenergic (sympathetic) fibers* do not stain readily and hence their terminations have not been followed in detail. It is believed largely on the basis of physiological *investigations that they are distributed to the sino-atrial and atrial-*ventricular nodes, to the more peripheral parts of the conducting system, to both atria and ventricles and to the coronary vessels. *These findings suggest the possibility of nervous control over myocardial* contraction. In addition the abundance of such nerves found in proximity to or ending on the coronary vessels implies a probable vasomotor function.

half of the interventricular septum and a large part of the posterior wall of the left ventricle. About a third of the hearts have a balanced coronary circulation in which each of the heart's two ventricles receives its blood supply from its *corresponding artery, i.e.*, the right coronary artery supplies only the right ventricle and the posterior half *of the interventricular* septum and the left coronary artery supplies the left ventricle and the anterior half of the *interventricular septum*. Approximately a fifth of the hearts are left coronary artery *predominant*. In these the left coronary artery may supply the whole of the left ventricle and the *entire interventricular* septum anteriorly and posteriorly. In addition to the left ventricle and the *entire septum* it may also supply a part of the right ventricle over its *posterior* surface and anteriorly in the region around the pulmonary conus and on the right ventricular side of the left descendens.

The coronary arterial pattern of the dog's heart is *quite constant and compares* with the left coronary predominant heart in *man*.[76, 9] The *close resemblance* of the coronary artery pattern in the dog's heart *to the* human heart which suffers *most* from the effects of arteriosclerosis, *i.e.*, the left coronary artery predominant heart,[40] necessitates caution in transferring to the human heart results and conclusions arrived at by *interference* with the circulation of the dog's heart.

In *man* the sino-atrial node is supplied by a branch of the right coronary artery (*near its ostium*) in about 70 per cent of hearts,[7] and by a branch of the left coronary in 25 *per cent* and in 7 per cent from both vessels. The atrial ventricular node is supplied by the right coronary in about 92 per cent of hearts. The right bundle branch generally obtains its blood *supply* from the anterior *descending* branch of the left coronary artery but may be supplied by both right and left coronary *arteries*. *The left bundle* branch is generally supplied by both arteries, usually from septal branches of the left anterior *descendens* branch and small vessels from the right coronary artery. The arborization systems receive their blood from arteries supplying the myocardium in which they lie.[2, 3, 4, 14, 15, 43, 51]

B. **Capillary Bed.**—Because of the great difficulty of their injection few studies have been made of the capillaries of the heart. Wearn and co-workers[28, 29, 4, 49, 50, 52] using an *injection* technique for the isolated revived human, cat, and rabbit heart, succeeded in injecting most of the capillary bed with an oxygenated Locke-Rosenheim solution containing blue dye. An example of such injection is illustrated in figure 7. By such injections the small arteries and arterioles are found to lie in the spaces between and parallel to the muscle bundles. The *arteriole* pierces the muscle bundle, usually

coronary branches are carried along with the muscle to supply the inner layer of both ventricles and the papillary muscles Gross dissection, injection, and studies of the distribution of myocardial scars in the dog and human heart strongly suggest that each ventricular muscle bundle has an individual blood supply, although as shown in figure 5 numerous communications exist between the different muscle layers [0 1 3 3]

The general pattern of distribution of the coronary arteries and their branches is far from constant in man [40 41] By roentgenographic visualization of the coronary arteries injected with lead phosphate

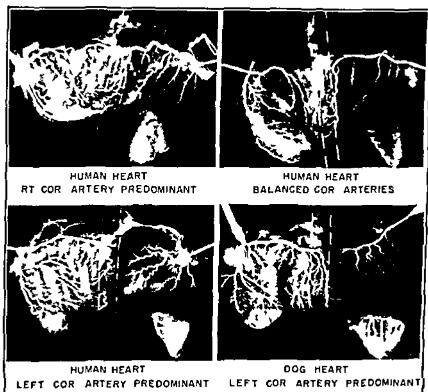


FIG 6 —Distribution of coronary arteries of human and dog heart (Schlesinger [40])

agar, and in hearts unrolled before fixation so as to flatten out the coronary arteries in one plane human hearts have been found to have three distinct patterns of distribution of their arteries right coronary artery predominant left coronary artery predominant and a balanced coronary circulation *These are shown in figure 6* About half the hearts are right coronary artery predominant *i e* this coronary artery supplies all of the right ventricle the posterior

either continues in the muscle bundle for a short distance, runs directly across and perpendicular to the fibers to the spaces between the muscle bundles, or occasionally drains directly into the heart chambers.

At birth, the myocardial fibers have a diameter approximating 6 to 9 microns and with growth of the heart to an adult size the fiber diameter increases to approximate 12 to 15 microns (Fig. 8).

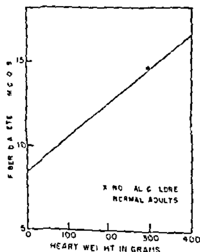


Fig. 8.—Relation of fiber diameter to heart weight. (Wearn.)

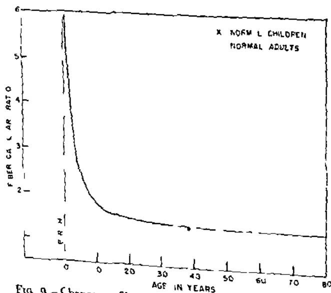


Fig. 9.—Changes in fiber-capillary ratio with age. (Wearn.[32])

diagonally or transversely, and immediately arborizes into capillaries which are parallel to and in contact with the muscle fibers (Fig 7) Capillary anastomoses are very frequent and form plexuses of vessels through which the branching cardiac muscle fibers run From the boundaries of these capillaries arise the lymph channels which drain into a subepicardial meshwork of lymphatics [6] At their venous ends the capillaries suddenly converge to form a small venule which

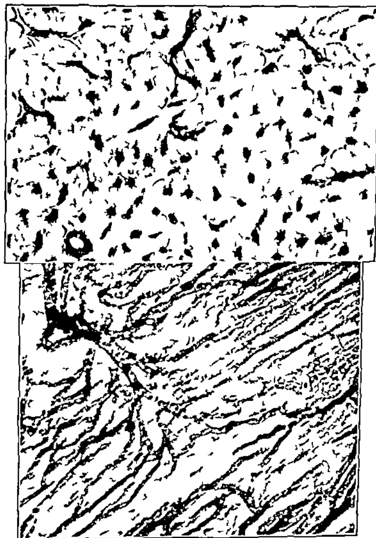


Fig 7 —*Upper* photomicrograph of a cross section of heart muscle fibers showing capillaries injected with Berlin blue × [illegible]00 *Lower* photomicrograph of a longitudinal section of heart muscle showing a small arteriole arborizing also numerous anastomoses between the capillaries The capillaries lie alongside each fiber × [illegible]00 (Wearn[51] courtesy of the Macmillan Co)

C **The Venous Bed** — The venous drainage systems of the myocardium are (*1*) the superficial or subepicardial system which empties into the right auricle and consists of the anterior cardiac veins and the coronary sinus together with associated veins emptying near its mouth and (*2*) a deeper system of veins which communicates directly with the heart chambers

The superficial drainage system of coronary veins extend over the surfaces of the heart The greater portion of the subepicardial surface of the left ventricle is traversed by many small venous branches which merge to form the larger coronary veins These in turn converge to form the coronary sinus which with the asso-



FIG 11 —*Upper Left* Roentgenogram of heart in which the four major anterior cardiac veins have been cannulated and injected with contrast medium Anterior view *Upper Right* Roentgenogram of heart in which three branches of one anterior cardiac vein have been injected Anterior view *Lower* Photograph of interior of right atrium showing the position of four major anterior cardiac vein openings with plugs of injection material remaining after removal of cannulae The arrow points to the opening of the vein which drains the pulmonary conus region (Gregg *et al* [13])

The capillary counts are considerably higher in the ventricles than in the auricles and the neuromuscular bundle. At birth, there are about 5 to 6 muscle fibers to each capillary. As the muscle fibers increase in size through growth the fiber-capillary ratio decreases progressively to approximate one capillary for each muscle fiber (Fig 9). Throughout the growth period the concentration of capillaries per unit area is maintained at a fairly constant level (approximately 4,000 per square millimeter). Thus the increase in muscle mass is accompanied by an increase in total number of capillaries. After full growth the normal hearts of adults (twenty five to seventy seven years) maintain an approximately constant capillary concentration and the muscle fibers remain at the same size so that the fiber-capillary ratio is maintained (Fig 9).



Fig 10 — Photograph of dog's heart showing the distribution of superficial veins over the surface of the right ventricle (Gregg et al [11])

branches of coronary arteries were found to leave the heart around the ostia of the pulmonary vein and artery, the superior and inferior vena cava, the root of the aorta, and in the intrapericardial reflections and then anastomose with the internal mammary artery and various aortic branches so that blood is distributed to the vasa vasorum of the thoracic aorta and pulmonary artery throughout the pericardium, diaphragm, pleural surfaces of lungs, the bronchi, mediastinum, trachea and esophagus.[17]

It is easy to demonstrate in the normal heart that anastomoses exist between the coronary arteries and/or their branches. Watery solutions of India ink, Prussian blue, or saline suspensions of red cells labeled with radioactive phosphorus when injected into a coronary artery or branch quickly appear in the other coronary artery.[24,31] However, the use of such low viscosity substances does not indicate the probable size of the communications either in death or

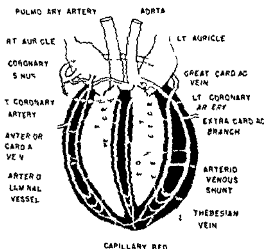


FIG 12 —Schematic drawing of heart indicating principal circulatory channels

life. Estimates of the size and extent of these intercoronary artery communications in the normal heart is controversial. By the injection into one coronary artery of radiopaque media such as barium sulphate or lead agar which is too thick to penetrate the capillaries these communications were found to extend up to at least arteriolar size.[15,40] However, in the dog heart it was only an occasional finding to have a second coronary artery filled with the injection material and only 12 per cent of normal human hearts were found to have interarterial communications of thirty to eighty micra in di-

cated veins emptying near its mouth constitutes the major superficial drainage system of the left heart. In the right heart, the small venous branches merge to form the anterior cardiac veins, anatomically the lesser of the superficial venous systems.[13] These are illustrated in figure 10. They constitute several good sized venous trunks which lie buried in the subepicardial fat occupying the sulcus between the right auricle and right ventricle and each generally empties separately and directly into the right auricle a few millimeters superior to the ventricular border of the tricuspid valve (Fig 11). Other smaller veins are invariably present. The anterior cardiac veins, although described by Grant,[10] have been virtually ignored by physiologists. The blood supply to the vessels of the heart is considered in Chapter 8.

D **Collateral Channels.**—The collateral channels of the artery capillary vein system of the heart are numerous and complex and include arterio luminal vessels, arterio sinusoidal vessels, Thebesian veins, and intra- and extra-cardiac anastomoses of arteries, veins and capillaries. These are shown schematically in figure 12.

Communications between the coronary arteries and the cardiac chambers were first demonstrated in 1706 by Vieussens.[46] From injections of the coronary arteries with celloidin too thick to pass through capillaries, then digesting off the myocardium and making wax reconstructions from serial sections of such vessel casts, two types of vessel were found connecting the coronary arteries with the atrial and ventricular cavities. Each starts as an arteriole arising from a small coronary arterial branch. The one type (arterio luminal vessel) loses its arteriolar structure as it approaches the lumen of the heart. The other and more numerous type (arterio-sinusoidal vessel) gradually loses its arterial character while still deep in the myocardium and breaks up into large, irregular channels or simple endothelial tubes resembling the capillaries in structure.[53]

Thebesian veins are collateral channels between the distal ends of capillaries or coronary veins and the heart chambers. They were first described by Thebesius[44] and their presence and frequency were confirmed by many investigators.[11, 50] They are more numerous in the right ventricle than in the left.

In addition there are numerous anastomotic channels connecting the coronary veins of auricles and ventricles with each other, with Thebesian channels and with extracardiac veins draining into the superior and inferior vena cava.[1]

Not much has been written about the anastomoses of branches of the coronary arteries with vessels outside the heart since von Haller[47] first mentioned them. By injections into the coronary arteries,

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ameter[1, 41] More recently, injection of graduated glass spheres and radioactive red cells into the coronary arteries of normal human hearts indicates that the largest intercoronary artery communications range from 70 to 180 micra (approximately the diameter of arterioles) and some of these can be seen visually in the normal heart[31] Using similar methods, Thebesian, arterio-luminal and arterio sinusoidal channels were found to range from 70 to 220 micra and arteriovenous channels from 70 to 170 micra The size of these communications in the two ventricles is about the same[31] Obviously, *these observations do not necessarily indicate the size of the* communications during life These intra- and extracardial communications (illustrated schematically in figure 12) while small are *numerous and collectively make an anastomotic channel of considerable diameter* With appropriate stimuli, both arterial and venous *anastomoses may become greatly enlarged*[1, 17, 4, 5, 5]

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Chapter 3

EXPERIMENTAL APPROACHES TO THE CORONARY CIRCULATION: PREPARATIONS; CARDIAC PRESSURES AND THEIR DETERMINATIONS

The solution of problems dealing with the coronary circulation depends upon the development of adequate preparations and methods and the overcoming of instrumental difficulties. Such consideration should reveal in part the proper basis for the interpretation of past and future studies of the coronary system.

PREPARATIONS

Much information has been gained from experimental preparations in which the coronary circulation has been studied with the heart in various degrees of separation from the rest of the animal. These preparations include the heart lung, the isolated heart with or without an artificial lung, and the fibrillating heart. In almost all phases of modern cardiac research, at least the initial experiments were performed using one of these preparations, and most of the concepts thus established stand today.

The use of the isolated perfused heart by Langendorff[40] in 1895 and by Porter[51] in 1896 laid the groundwork for our understanding of the fundamentals of the coronary circulation. Originally the heart was suspended and the coronary arteries perfused under constant temperature and pressure with oxygenated saline through a cannula in the aorta which was directed toward the aortic valves. Total venous return was measured by overflow from the right atrium and ventricle. With this procedure, studies have been made not only in animal hearts but also in human hearts by Kountz et al.[36,37] To obviate the effects of cardiac contraction and thus reduce the number of uncontrolled variables, the perfused quiescent or arrested heart was used by Wiggers[64] in 1909 and more recently the fibrillating heart by Katz, Weinstein and Jochim[33] in 1935. In the different experiments the coronary arteries were perfused under a constant pressure or with the naturally pulsating aortic pressure.

The development of the heart lung preparation by Starling[35] and Evans[9] in 1912 and its subsequent use by Anrep[1], Visscher[59], Katz[34] and Gollwitzer-Meier[14] has probably contributed more to

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coronary sinus flow (times a factor), and the oxygen arteriovenous difference in the coronary blood

In general the experimental findings with these preparations have been considered significant and applicable to the normal heart beating *in situ* The chief advantage in using such preparations is that the several variables such as peripheral resistance, arterial and venous pressure and cardiac output can be more easily controlled and the coronary flow more easily measured but the part each plays in the intact animal is unknown It is justifiable to determine by this means what can happen with the hope of ultimately learning more about what does happen in the intact animal

Wiggers[56] in 1912 was one of the first to use the heart beating *in situ* in the anesthetized dog with open chest and in which the coronary vessels were naturally perfused from the aorta using some of the devices and methods to be described in subsequent chapters This should be a closer approximation to the normal animal involving a lesser insult to the animal s own nervous metabolic and cardiodynamic mechanisms The use of this controlled preparation together with the closed-chest anesthetized dog has been largely expanded by associates and pupils of Wiggers Some of these studies presumably indicate with reasonable exactness changes which occur in the normal animal Even so these preparations cannot be regarded as normal and the observations can be accorded only a limited interpretation

While none of these preparations is regarded as entirely adequate for studying the heart and coronary circulation still it is informative to indicate the comparative findings In most instances the findings are similar in the heart lung preparation and in the heart beating *in situ* These are considered in detail in subsequent chapters but they are briefly indicated here The findings in the two preparations are similar in that left coronary inflow drains by the coronary sinus most drugs have a similar action on coronary flow an increase in coronary perfusing pressure stimulation of sympathetic fibers to the heart asphyxia anoxia and ischemia all increase left coronary inflow systole of the left ventricle coronary sinus occlusion and vagus stimulation decrease left coronary inflow while systole of the left ventricle and augmentation of right or left ventricular pressure increase coronary sinus outflow However a portion of the work with the heart lung preparation may have only a limited significance for in some instances the findings are not comparable When compared to studies with the heart beating *in situ* the contours and values of the pressure curves are different the volume of coronary inflow and the coronary oxygen A V difference are generally greater while the

our knowledge of the heart and coronary circulation than any other preparation or experimental approach. In this preparation the lungs and heart are removed without interruption of the blood supply, the blood is defibrinated or an anticoagulant added and the systemic circulation is replaced by an artificial resistance which can be varied at will, thus giving a wide range of arterial pressure. After passing this resistance blood enters a reservoir from which it returns to the right atrium at a rate controlled by an adjustable screw clamp so that the venous return to the right ventricle is controlled. The pulmonary circulation is not interrupted and arterialization of the blood is accomplished by the lungs, or the blood may be passed through a specially devised oxygenation apparatus.[31] To more nearly approximate the normal physiological environment, the heart and lungs are removed in such a way that the cerebral circulation remains connected to the heart, and the vagal and sympathetic nerves of the heart remain intact.[14] Thus heart rate, venous return, cardiac output, aortic and pulmonary artery resistances, atrial pressures, temperature, and the chemical composition of the blood can be separately altered and controlled.

Early in this work, Morawitz and Zahn[46] developed a cannula for insertion into the coronary sinus via the right atrium. The flow through it was presumed to quantitate total venous return from the vessels of the heart. This investigation was important because it enabled the experimenter to study coronary flow with the beating heart *in situ* as well as in the isolated heart preparation. However, experimental work soon showed that the coronary blood drained by this channel represented only a fraction of the total coronary venous outflow. The reliability of the use of the method, therefore, depends upon the constancy of the fraction drained through the coronary sinus. Starling and his associates[10,45] employed the cannula to measure coronary venous outflow and assumed that it represented a relatively constant fraction of coronary inflow. Somewhat later Anrep and his associates[3] in 1926, Katz[34] and others cannulated both coronary arteries, supplied them with blood under a constant perfusion pressure and measured coronary inflow under a great variety of dynamic conditions.

For studies of the metabolism and work of the heart, the heart-lung preparation was early used. The metabolism was originally measured by attaching to the trachea a metabolism outfit which quantitated the oxygen consumption. To eliminate the metabolic effects of the lungs, the heart was connected to an artificial lung by Evans[11] in 1934. The Starling group also calculated values for the level of cardiac metabolism and work from measurements of the

manometer shown in figure 13 has been used in the author's laboratory for many years. This is similar to that devised by Hamilton except that a special rubber (or mica) membrane is generally used and its mechanical features permit great ease of adjustment and flexibility in use. A glass spoon manometer has been devised which is easy and cheap to make.[illegible] In addition, a glass membrane manometer has also been found useful.[illegible]

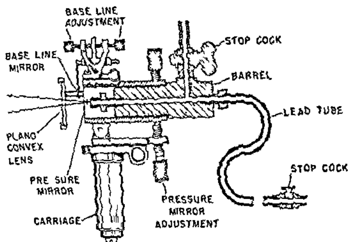


Fig. 13.—Gregg manometer, somewhat modified from original model.[illegible]

The requirements of an adequate membrane manometer and the means to attain it have been considered in detail by Wiggers[51] and will be alluded to only briefly here. To follow the details of a rapidly fluctuating pressure in the cardiovascular system with a membrane manometer, the pressure recording system must have a sufficient sensitivity so that the recorded curve will be sufficiently large to indicate changes in gradient, and yet it must be capable of following the pressure fluctuations with minimal distortion and without measurable lag.

Sensitivity is a static characteristic of a manometer which enables the investigator to read the curves more easily, but it is not concerned with the correctness of the recorded curve. Manometer sensitivity, or the relation of the magnitude of the deflection to the applied pressure, can be increased by decreasing the tension of the membrane or its thickness, by increasing the diameter of the opening at the tip of the manometer, by increasing the distance of light beam projec

cardiac output, metabolism, work and efficiency are considerably less In addition, in the heart-lung preparation, a considerable portion of right coronary inflow drains by the coronary sinus while with the heart beating *in situ*, very little apparently leaves by this channel Most of right coronary inflow drains by the anterior cardiac veins with the heart *in situ* while in the heart lung preparation, this has not been demonstrated Finally elevation of left or right ventricular pressure does not generally increase coronary inflow in the heart lung preparation but does so with the heart beating *in situ*

The ultimate objective is the quantitative measurement from moment to moment of the indicated activities of the coronary circulation and heart, and the study of the various determinants in the normal, unanesthetized animal and human subject Final judgment as to the validity of many of these accepted conclusions based on the aforementioned preparations, must await extensive reinvestigation in which utilization is made of the heart beating *in situ* in its normal environment Although exploratory and preliminary studies are reported in which some of the laboratory methods and procedures are being applied to unanesthetized dogs and human subjects as yet they have not been sufficiently checked so that their ultimate value for the determination of coronary pressures and flow cardiac metabolism output, work, and efficiency in such a situation is not known

PULSATILE CARDIAC PRESSURES

Information concerning the moment to moment changes in pressures within the coronary vessels cardiac chambers, and myocardial walls is vital for the interpretation of the essential mechanisms by which the coronary flow is altered and the myocardium nourished since they are the dominant factors in determining coronary flow, work and metabolism Accordingly, appropriate means for their determination are considered in some detail

Manometers Used and a Consideration of Their Adequacy — Most of our fundamental knowledge concerning cardiac pressures has been obtained with the use of the early optical membrane manometers devised by Frank[1] and Wiggers[69] Since these original glass optical manometers with rubber membranes were devised others have been developed to provide greater flexibility in use and greater instrumental frequency without sacrifice of sensitivity[21,76] Each has advantages and disadvantages The Hamilton manometer uses a metal membrane and long lead tube to attain a high frequency but its mirror and light beam are adjusted with difficulty The

that a frequency of 100 to 125 per second is adequate to record accurately a pressure curve from this cavity in the anesthetized open-chest dog. The requisite manometric frequencies have not been determined for the other cardiac regions or for the left ventricle with the animal in the unanesthetized state.

In addition to low instrumental frequency, hysteresis may cause failure of the light beam to follow accurately the pressure changes. This may be in the membrane or in the material used to mount the mirror on the membrane and is generally avoided through making quite small the point of contact between the membrane and mirror by inserting between the two surfaces a very thin short pedestal which is mounted with a rigid cement which adheres well to both.

One of the best optical systems for recording purposes is that designed by Hamilton [8] and with the *modifications indicated* is used in the author's laboratory (Fig. 14). Light from the filaments of a

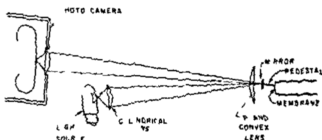


FIG. 14. Optical projection system used by author, somewhat modified from that of Hamilton.

projection bulb impinges on a plano mirror (a chip from a certified bureau of standards counting *chamber* cover slip or a rhodium first surface mirror). The beam is focused *on a camera* by a plano-convex lens of appropriate diopter *placed* immediately in front of the plano mirror. To lengthen the *vertical light beams* at the camera, a cylindrical lens is inserted in the light path near its source. Time is indicated by an *electrically operated tuning* fork, a Jaquet chronometer or by interrupting the light beam with the spokes of a wheel attached to a synchronous motor.

These membrane manometers *have* the disadvantages that rigid connections are *necessary* between the animal and the recording system, fixation of the diaphragm relative to the recording device is necessary, the sensitivity *is not easily* adjusted during an experiment, and a high sensitivity with adequate frequency necessitates a long projection distance to the camera.

tion, and by optimal placement of the pedestal on the membrane

The accuracy with which a manometer indicates the pressure fluctuations and the physic relations of pressure is dependent on the natural frequency of the manometer ensemble In practice this is determined by recording the membrane oscillations which occur when a pressure applied to the membrane is suddenly released This *is expressed by* $N = \frac{1}{T}$ *in which* N *is the number of double* oscillations per second recorded and T is the duration of a double vibration

The natural frequency (N) of a manometer system in cycles per second is dependent on controllable variables and can be calculated from the volume elasticity (E) and the *effective mass* (M) *of the* system, thus

$$N = \frac{1}{2\pi}\sqrt{\frac{E}{M}}$$

The volume-elasticity or the ratio of pressure increase to volume increase $\frac{(\Delta P)}{(\Delta V)}$ is determined by the pressure required to move a unit volume of fluid into the manometer system The effective mass is a measure of the inertia of the system and varies directly with the length of the manometer tubes, and inversely as their mean cross-sectional area

From the preceding it is apparent that the best manometer is the one with the lowest effective mass and the greatest volume-elasticity The former is attained by using the shortest and widest liquid column and the latter by use of the most rigid membrane by use of non-distensible material for the manometer wall and the elimination of bubbles from the manometer system The manometer used is generally a compromise between maximum sensitivity and minimum curve distortion allowable for a given pressure recording The actual sensitivity is determined by the magnitude of the pressure variation to be recorded In general the sensitivity is greatest for the pressure curves from the coronary veins and atria least for the curves from the aorta, left ventricle and myocardial wall, and intermediate for curves from the pulmonary artery and right ventricle The necessary manometric frequency for pressure recording will vary with the different regions from which the pressure is recorded Theoretical and practical tests have demonstrated that a manometer has a sufficient frequency when the ratio of its natural frequency to that of the shortest frequency component which enters into the pressure variation to be recorded is four to five By harmonic analysis of a left ventricular pressure curve it has been established

pick up end of the manometer, and by momentary partial or complete occlusion of the manometer opening. The manometer carriage and its pressure pick up end together with the intervening lead tube connector must be rigidly fixed to avoid gross deformation of the pressure curve. Cardiac movements are especially apt to affect the pressure curve at those periods of rapid changes in pressure, i.e., at the beginning of contraction, at the beginning of ejection, and at the beginning of filling of the heart in diastole. These appear as jogs or vibrations on the ascending and/or descending limbs of the pressure curve. Despite all precautions, it is often impossible to obtain technically perfect records in hearts in a good dynamic state. Because of their extreme importance in relation to the coronary circulation, the experimental approaches and techniques used, the criteria of normal curves obtained from the various cardiac regions, and the indicated normal curves are considered.

For the registration of aortic pressure in the morphinized, closed chest dog, the manometer trocar is thrust down a carotid artery into the aortic arch. In the open-chest dog, the same approach may be used or the trocar may be inserted through the brachiocephalic artery. Left intraventricular pressure is recorded most satisfactorily by thrusting a trocar or needle attached to a recording manometer *directly through the ventricular wall*. In the open-chest animal this approach offers no great difficulties. With care, the needle can also be inserted through the closed chest into the left ventricular cavity. However, the danger of puncturing a coronary vessel within the closed chest is always present. This can be avoided by a previous operation in which the left apex is sutured to the chest wall.[23]

At least two views have been held concerning the normal relationship between left ventricular and aortic pressure curves as regards contour and *ordinate value*. The one sponsored by Wiggers[37] on the basis of experiments on anesthetized dogs with open chest, and subscribed to by most investigators, holds that the systolic portions of both curves are parallel and have essentially the same ordinate values, whereas the other, sponsored by Hamilton and associates,[23] maintains on theoretical and experimental work with unanesthetized dogs that, during systole, the apical intraventricular pressure must and does exceed the aortic to insure that blood will flow from the ventricle to the aorta. Failure to obtain curves showing such pressure differences (indicating low or zero velocity in the ventricular apex and high velocity in the aorta) is ascribed to various factors which tend to reduce the kinetic factor and hence minimize the excess ventricular pressure; these include reduction of cardiac output through anesthesia and surgical shock and connection of the intra

Some of the disadvantages of the mechanical optical manometers can be overcome by electrical translation in which the membrane, lead tube, cannula, or hypodermic needle connection to the pressure source is generally retained and an electrical system is placed between the membrane and the recording system. This has been accomplished by different investigators in the following ways: (1) Retaining the mirror membrane and having the mirror light activate a photocell [13] (2) eliminating the mirror and reflecting the light directly from the polished diaphragm surface into a photocell,[33] (3) measuring the change in resistance in a magnetic field of bismuth coils on the diaphragm,[7] (4) allowing the diaphragm to act as the movable plate of an electrical capacitance and measuring the variations in capacity by means of a radio frequency circuit [41, 4, 50] (5) having the moving diaphragm induce voltage changes in a Rochelle salt crystal which is connected to it [44] (6) elimination of the membrane and having the pressure in the manometer tube activate a strain gauge [39] (7) having the pressure within the manometer tube alter the magnetic reluctance between two coils by moving a membrane between them and thus creating an electrical imbalance of a bridge [8, 47]

In these various electrical systems after suitable amplification the pressure changes may be indicated by an optically recording galvanometer, oscilloscope, or ink-recorder. It is not believed that any of these devices has as yet been critically tested for its ability to accurately record pressure changes in cavities and vessels of the heart. While many of these devices may faithfully follow the correct pressures as indicated by comparison with direct recorders, their complexity and cost have thus far prevented their wide usage.

Technical Aspects of Cardiac Pressure Curves and Their Registration.—The fact that a recording manometer has an adequate frequency and sensitivity does not insure that the pressure records obtained with it are free of artefacts. In the evaluation of pressure curves, especially those from the cavities, walls and vessels of the heart, seemingly trivial variations in technique can cause large changes in the character of the record produced. In use, the manometer may be attached to a cannula, needle, or catheter which by lowering its volume elastic coefficient or increasing its effective mass, destroys its efficiency, or it may be placed in an almost impossible dynamic situation in which only by extreme care and in experienced, expert hands can technically good curves be obtained. Artefacts are generally introduced into the pressure curves through mechanical impact or movement of the cavity, muscle, or vessel from which the pressure is recorded by movement of the pressure

cannula or needle in the ventricular cavity. However, left ventricular pressure curves considerably in excess of the aortic and differing also in contour during systole can be obtained readily by inserting the ventricular needle so that fluid under pressure entering from the manometer runs through it very slowly, or not at all. Such impedance must arise from partial or complete occlusion of the opening during systole. Such curves are believed to represent technical artefacts and not true pressure variations in the ventricle.

Considerable controversy has arisen and still continues concerning the contour of the aortic and left ventricular pressure curves which best represents the normal hemodynamic state. From the examination of a great many records obtained in lightly morphinized dogs and in trained unanesthetized basal dogs in which the left ventricular apex was sutured to the chest wall, the record in figure 15 (left) was selected as best portraying the normal type of pressure curve in aorta and left ventricle. Since these pressures are somewhat higher than those in a basal dog, the left ventricular pressure curve in figure 15 (right) is included. In the latter the dog was trained and unanesthetized, the carotid pressure (not shown here) was taken from a Van Leersum loop and the ventricular pressure by needle inserted into the ventricle which had been previously sutured to the chest wall. The distinguishing feature in figure 15 is that the ventricular curve (and the aortic) have a sharply rising plateau during systolic ejection. Curves with a smoothly rounded and arched systolic summit, such as described by Wiggers[37] as normal for the open-chest dog, are easily and often obtained in that preparation and actually were recorded in the experiments of figure 15 following general anesthesia and opening of the chest. However, such curves are believed to represent a somewhat hypodynamic state in which the vigor of left ventricular contraction, the cardiac output and degree of aortic filling are all somewhat reduced.

Pressure in the pulmonary artery has been taken in the anesthetized open-chest state by a cannula inserted directly through the conus arteriosus with fixation by a fine purse string suture, by a cannula inserted into a pulmonary artery branch, or by needle puncture.[57] In the unanesthetized or anesthetized state, pulmonary artery pressure has been taken through a catheter inserted into it via the antecubital[8] or jugular vein,[59] or by needle puncture through the chest wall, the needle being guided by a London cannula placed at a previous operation and connecting the pulmonary artery and chest wall.[7,8,43] For right ventricular pressure recording the same approaches as for the left ventricle are used. In addition, pressures

ventricular manometer to the upper portion of the ventricle, a region in which the blood has nearly attained the aortic velocity.

In figure 15 (left) are shown comparative records of left intraventricular pressure and aortic pressure from the author's collection taken in the morphinized dog. The left ventricle was entered laterally by a 20 gauge needle, and the arterial pressure was obtained from the aorta by means of a long trocar pushed down the carotid artery (after its exposure under procaine) to the aortic valves. The manometers differ only slightly in sensitivity. A normal sinus arrhythmia is present with the heart rate varying from forty to eighty per minute. During diastole the ventricular pressure rises slightly to reach 15 mm Hg just before atrial systole at A. It rises steeply during the ventricular isometric contraction period (C D),

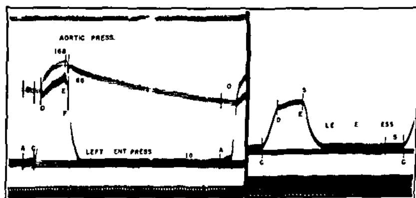


Fig 15.—Records of aortic pressure and left intraventricular pressure taken from a morphinized dog (left) and a trained unanesthetized dog (right). In the latter the left ventricular apex had been sutured to the chest wall in a previous operation. Vertical intercepts denote: *A*, onset of atrial contraction; *C*, beginning of ventricular isometric contraction; *D*, opening of aortic valves; *E*, onset of protodiastole; *F*, closure of aortic valves. Time 0.02 sec.

and then more gradually but still quite rapidly and smoothly throughout the duration of systole to reach a peak of 166 mm Hg just before protodiastole at F. This is followed by a period of rapid pressure drop during protodiastole (E F) and the isometric relaxation period. The aortic curve parallels very closely that of the ventricle while the aortic valves are open with systolic and diastolic pressures of 168 and 108 mm Hg. (The difference of 4 mm Hg between the two systolic pressures is regarded as approximating the upper range of experimental error.) Such a relationship of contour and ordinate values has been found to hold regardless of the condition of the circulation[3] and irrespective of the location of the

cannula or needle in the ventricular cavity. However, left ventricular pressure curves considerably in excess of the aortic and differing also in contour during systole can be obtained readily by inserting the ventricular needle so that fluid under pressure entering from the manometer runs through it very slowly or not at all. Such impedance must arise from partial or complete occlusion of the opening during systole. Such curves are believed to represent technical artefacts and not true pressure variations in the ventricle.

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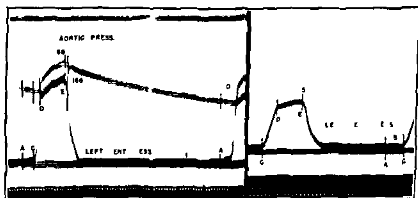


Fig 15 —Records of aortic pressure and left intraventricular pressure taken from a morphinized dog (left) and a trained unanesthetized dog (right) In the latter the left ventricular apex had been sutured to the chest wall in a previous operation Vertical intercepts denote A onset of atrial contraction *C* beginning of ventricular isometric contraction *D* opening of aortic valves *E* onset of protodiastole *F* closure of aortic valves Time 0 02 sec

and then more gradually but still quite rapidly and smoothly throughout the duration of systole to reach a peak of 166 mm Hg just before protodiastole at F This is followed by a period of rapid pressure drop during protodiastole (F-F) and the isometric relaxation period The aortic curve parallels very closely that of the ventricle while the aortic valves are open with systolic and diastolic pressures of 168 and 108 mm Hg (The difference of 4 mm Hg between the two systolic pressures is regarded as approximating the upper range of experimental error) Such a relationship of contour and ordinate values has been found to hold regardless of the condition of the circulation [3] and irrespective of the location of the

chest dog Even with the use of large infusions of blood or with pulmonary artery constriction leading to an elevation of the systolic pressure in the right ventricle to 80 mm Hg the contours do not show a rising plateau during systolic ejection but remain similar to those in the curves shown here[13] Presumably this indicates that the peripheral resistance in the pulmonary artery and its extensions is quite small as compared to that in the aorta and its vascular bed

Other patterns of the right ventricular pressure pulse have been obtained An example of the most common of these is the tracing in figure 16 (upper right) taken in the author's laboratory from a normal unanesthetized dog with an adequate needle membrane manometer system As compared to the other right ventricular curve in figure 16 the declining pressure precipitously drops to values less than zero early in diastole and just after the opening of the tricuspid valves Curves of this type have also been obtained in the open-chest dog by Katz[30] using the Wiggers manometer and in the right ventricle of human subjects[4] in which the pressure was taken through a catheter attached to a Hamilton manometer By itself this descent of the declining pressure curve to values below zero indicates that the right ventricle exerts a suction action a theory first proposed by Goltz and Gaule in 1878[18] and subsequently adhered to by many physiologists However the fact that in the dog this type of right ventricular pressure curve can be easily converted to that in the lower left in figure 16 by adjustment of the needle or cannula and that right ventricular curves obtained by ventricular puncture through the chest wall in humans display no such abnormality[5] is strong evidence that this portion of the pressure curve is an artefact

Although the artefact just described can occur with the use of a needle or trocar attached to an adequate pressure manometer as well as with the use of a catheter the use of the latter tube in association with an adequate manometer offers the possibility of introducing certain other error arising from the free movement of the catheter Right ventricular pressure curves recorded through the latter often have additional deformations of their ascending and descending limbs as compared to ventricular pressure recorded through a needle connected to an adequate manometer By critical damping of the manometer-catheter system the ordinate values and contour of the pressure curve obtained from the right ventricle have been found to compare favorably with those simultaneously taken with a manometer needle or trocar system[42] However such damping merely substitutes one error for another for now a considerable time lag is thereby induced

may be taken from the right ventricle by a catheter or plastic tube inserted into it via the antecubital vein under fluoroscopy [6]

Technically adequate tracings of pressure variations within the pulmonary artery and right ventricular cavity are not too difficult to obtain in the open-chest dog or in the normal unanesthetized dog or human subject Figure 16 illustrates the pattern of curves that has almost invariably been obtained in the author's laboratory in the trained unanesthetized dog by direct needle puncture In the lower (right ventricular) curve the tracing starts as a small hump representing atrial systole The curve then rises steeply and without interruption to a rounded systolic summit The curve then descends smoothly in early diastole to approximate a zero pressure level, and

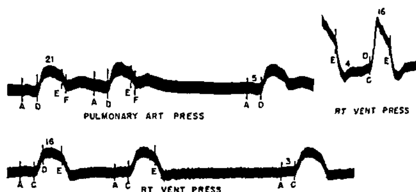


FIG 16 —Pressure curves from the pulmonary artery and right ventricle of trained unanesthetized dogs by direct needle puncture Upper left *pulmonary artery curve Lower right ventricular curve Upper right* right ventricular curve showing early diastolic artefact Vertical intercepts and letters same as in figure 15

then rises slowly throughout the remainder of diastole In the upper left (pulmonary artery) curve taken in a second unanesthetized dog by a needle inserted through the chest into the pulmonary artery just beyond the pulmonary valves the tracing also has a smoothly arched appearance during systolic ejection following which the dicrotic limb falls considerably to the incisura After a short rise in early diastole the curve gradually declines throughout the remainder of diastole As compared with curves recorded from the left side of the heart in figure 15 the curves do not have a rising plateau during systole but rather have a rounded summit or at times a declining plateau As in the left heart the pulmonary artery curve during systolic ejection faithfully follows its intraventricular pressure curve These curves are generally similar as regards relative contour to those obtained by Wiggers[57] and others in the anesthetized open

nected to a trocar or catheter thrust into it by way of a carotid artery [3] The pressure in either right or left atrium may also be picked up in the open-chest animal through a cannula inserted into it by way of the azygos vein or a branch of the pulmonary vein [4] respectively

An illustrative curve taken from the left atrium in the anesthetized open-chest dog is in figure 17 During atrial systole a rounded or somewhat peaked positive pressure wave B is invariably present Atrial contraction is essentially over at point C which signals the onset of ventricular contraction During ventricular contraction and up to the time of opening of the tricuspid valves shortly after I the atrial pressure values and pattern are grossly altered by artefacts These consist of a spike at the isometric contraction period of the right ventricle a marked reduction in atrial pressure throughout most of ventricular contraction occasioned by a downward movement of the base of the heart and oscillations at D and L associated with the first and second heart sounds Although the curve is deformed by artefacts still dynamic events can be interpreted so long as the curve at the B C and F points which correspond to the peak of atrial systole onset of ventricular contraction and beginning of ventricular filling respectively are well defined However it should also be obvious that if in the presence of such artefacts *mean* atrial pressures are recorded under different dynamic circumstances the values may be considerably in error as regards magnitude and they can well [illegible] to indicate even directional changes in pressure unless the actual level of pressure is altered greatly

The contour of the right atrial pressure pulse is fundamentally the same as the left showing the same waves but the waves in the right atrium are generally smaller in amplitude (See also Fig 17)

The pressure pulse recorded from a coronary artery is essentially the same as that recorded from the aorta just beyond the aortic valves The only difference is that just prior to the elevation of aortic pressure a small temporary augmentation of central coronary pressure generally occurs which has its origin in the peripheral coronary vessel This was first shown by Wiggers and Cotton[33] in 1933 A typical example from the author s collection is in figure 18 This demonstrates that the large superficial branches of the coronary arteries are distended during systole as are other arteries and negates the idea originally advanced by Stroem in 1707 that the coronary orifices are occluded by the semilunar flaps during systole

The pressure pulse in a coronary artery peripheral to a point of occlusion of the artery has been used as an index of the level of peripheral resistance in the coronary bed and of the functioning of ana-

Pressure pulses from the atria, and especially the right atrium are of particular importance in relation to the coronary circulation for almost all the blood returning from the coronary vessels in the atrial and ventricular muscles drains into the right atrium. Experimentally, the pressure in the right atrium in the normal or anesthetized state is determined by connecting an adequate manometer to a plastic tube[50] trocar,[54] (or a catheter[6]) inserted into the atrial cavity via the jugular or antecubital vein. In the anesthetized animal, the left atrial pressure is determined by a manometer con-

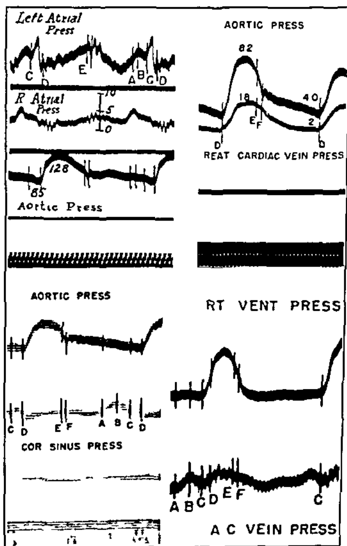


Fig. 17.—Pressure curves from the atria, coronary sinus, great cardiac vein and anterior cardiac vein in the open chest dog. B, peak of atrial systole. Other letters and vertical intercepts same as in figure 15, page 46. Time 0.02 sec.

four to six heartbeats until the pressure reaches an equilibrium. A typical record taken from the descendens branch of the left coronary artery after equilibrium had been established is illustrated in figure 18 (upper right). As compared to the aortic pressure simultaneously recorded, the peripheral coronary pressure at approximately the onset of the isometric contraction period starts to rise slowly at first (C), then more brusquely (C-D). This rise continues more gradually into the period occupied by the rise of the aortic pressure, then mounts as a gradually rising plateau to almost the end of systole (E). During protodiastole (E-F) the curve starts to decline, at first rapidly and then more slowly during the isometric relaxation phase. Just before ventricular inflow starts, the fall in pressure is essentially complete. The time relations and general features of the rise and fall correspond to changes of pressure within the left ventricle. The systolic and diastolic pressures thus recorded in the peripheral end of a coronary vessel are much lower than the corresponding pressures in the aorta. It is obvious that they do not represent the maximum pressure developed in the intramural vessel during ventricular contraction. The type of peripheral coronary pressure curve obtained in the right coronary artery following its occlusion is also illustrated in figure 18 (lower left). It is similar in pattern but less in magnitude than that obtained in a branch of the left coronary artery. These curves and their significance are considered in some detail in Chapter 8.

Presumably the phasic pressure existing around the coronary vessels and compressing them during a cardiac cycle is one of the most important determinants of coronary flow. Measurements of such intramural or intramyocardial pressure or extravascular support have been made by imbedding a vessel segment or fluid pocket in the wall of the left ventricle and recording the pressure change within it by an optical manometer.[7-9] Due to the thinness of the wall, such measurements have not been attempted in the myocardium of the right ventricle. A typical curve from the author's laboratory is shown in figure 18 (lower right). It will be observed that in this instance, with the vessel segment imbedded about one-half the depth of the myocardium, the resultant pressure curve has a smoothly rounded contour somewhat similar to the peripheral coronary pressure curve. However, it is believed that such curves have no counterpart in the normal left ventricular myocardium. The problem is considered in some detail in Chapter 6.

The pressure curves from the superficial veins of the heart are technically the most difficult to record. Pressure in a superficial vein of the left heart is picked up through a cannula inserted cen

tomotic connections [4] The pressure is generally recorded from a side branch of a coronary artery just distal to the region of occlusion Immediately following occlusion of a coronary artery or branch, the peripheral intracoronary artery pressure decreases progressively for

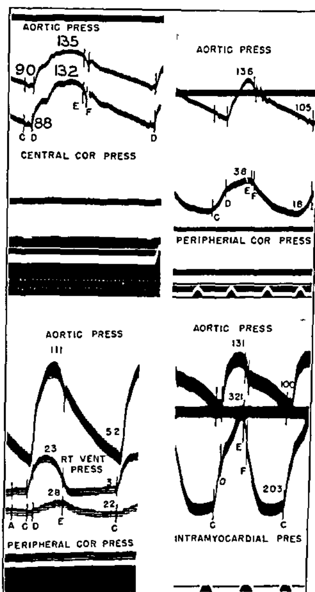


FIG 18 —Upper left simultaneously recorded pressure curves from the aorta and from a side branch of the ramus descendens branch of the left coronary artery Upper right pressure curves from same vessels but ramus descendens occluded central to the point of pressure registration Lower left peripheral coronary pressure curve from a branch of the right coronary artery Lower right aortic and intramyocardial pressure curve from the left ventricle simultaneously recorded Vertical intercepts and letters same as in figure 15, page 46 Time 0 02 sec 0 2 sec

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trally into a branch of the great cardiac vein [20] Pressure in the coronary sinus is taken by catheter,[17] it is also picked up by inserting and tying into it through the right atrial appendage a cannula which has a side opening permitting blood to flow into the atrium and almost at the mouth of which is a small lateral opening from which pressure is led through a small side tube to the recording manometer [9] Due to the small size of the anterior cardiac veins, pressure within them is measured by a small cannula with a drainage hole a few millimeters removed from the tip and inserted into an A C vein branch via the right auricular appendage, or the pressure may be picked up by cannulating centrally a branch of an A C vein [19]

Typical pressure curves obtained in the open chest dog in the author s laboratory from the great cardiac vein, the coronary sinus, and an A C vein are shown in figure 17 In the great cardiac vein the pressure curve has a smoothly rounded summit during systole which rises slowly during the isometric contraction period and then more rapidly during ejection and finally declines to its lowest level at approximately the beginning of atrial contraction

By the time this pressure pulse which has its origin deep in the myocardium has reached the region of the coronary sinus, its form is greatly altered The systolic rise is now largely missing and a pressure wave coincident with the time of atrial systole has been added The curve now resembles closely a right atrial pressure curve Similarly, the pressure curve taken from the ostium of an A C vein has essentially the same contour as that in the right atrium

It is hoped that this brief exposition concerning the adequacy of manometers to be used, and of the pressure curves obtained from the heart will aid in an understanding of the mechanism of operation of the coronary circulation

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Chapter 4

EXPERIMENTAL APPROACHES TO THE CORONARY CIRCULATION. CORONARY FLOW: ITS DETERMINATION

The direct quantitative determination of total coronary blood flow requires the measurement of flow in all the coronary arteries or veins. Flow measurements made in only one artery or vein may or may not indicate correctly the directional changes in total coronary blood flow. In general, when experiments are designed to permit measurement of total inflow or outflow, the preparation usually becomes sufficiently removed from the normal as to limit the interpretation of results.

The devices used may be divided into those which measure the phasic changes in rate of inflow or outflow and those which measure *mean rate of flow*. *From the phasic flow curves, mean rate of flow* can also be determined. Some of the devices are inserted between the severed ends of a coronary vessel or are inserted into an artery or vein at its mouth or exit and tied in place; others are applied to the external surface of the vein or artery and the flow is determined in the anesthetized or unanesthetized animal; in still another procedure flow is estimated by an adaptation of the Fick principle.

In using flow metering devices which must be inserted into a coronary artery, it is best that the coronary cannula be inserted into the brachiocephalic or into a carotid artery, then pushed down and into the left or right coronary ostium and tied in place,[5] as illustrated in figure 21. By this means total right or left coronary inflow is measured and the flow is not interrupted during the cannulation. The right coronary artery or a major branch of the left coronary artery *may also be cut and a cannula tied in place*.

PHASIC FLOW RECORDERS

Many of the various procedures and instruments have been considered in previous reviews.[1, 81] These methods were designed with the hope of analyzing the factors affecting coronary flow which are so rapid in action as not to be capable of effective study by mean flow measurements. For the measurement of the instantaneous changes in blood flow in the coronary arteries *and veins, the recording* device is designed to have a relatively high natural frequency

which permits optical recording of the rapid fluctuations in velocity of flow (flow pattern) These instruments record the instantaneous flow at the point of their insertion into a blood vessel The vascular bed of the heart is made up not only of vessels within the myocardial wall but also of vessels lying on the surface of the heart Since the change in mean bore during a cardiac cycle in the superficial vessels (in which the flow measurement is made) is presumably different from that of the deeper lying vessels such an instrument measures a combination of intramural and extramural flow It does not therefore necessarily indicate the corresponding flow at the same moment throughout the myocardium

The earliest attempts to measure phasic coronary flow although ingenious were necessarily crude and the results are consequently open to considerable question In 1899 Langendorff [37] by recording

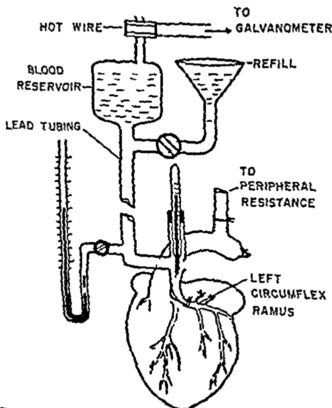


Fig 19 — Diagram showing principle of anemometer arrangement for measuring flow variations in left circumflex ramus Details in text (Anrep et al)

simultaneously the time of cardiac contraction and the rhythmical variations in coronary perfusion pressure in the isolated cat's heart predicted the phasic flow through the myocardium

The first of the precise methods was the adaptation in 1927 by Anrep, Cruickshank, Downing and Rau[1] of the hot wire anemometer to the measurement of coronary inflow and outflow in the denervated and innervated heart lung preparation The coronaries or a coronary artery, are perfused by blood from a reservoir which is elevated to produce the desired constant perfusion pressure, and in the mouth of which is placed a heated platinum wire[41] (Fig 19) As blood enters the coronary artery air flowing over the hot wire cools it, and properly calibrated records of its rate of cooling give a measure of phasic coronary inflow The height of the curve at any point gives the rate of flow and the area under any portion gives the volume flow Coronary sinus flow was also measured by cooling of the platinum wire when the reservoir was attached to the coronary sinus and kept at the heart level[1] Although this constituted a notable advance in the instruments available for studying the coronary circulation it is unable to indicate periods of retrograde or back flow it cannot follow some of the most rapid changes in flow and it has a considerable and variable time lag

Machella[39] in 1936 measured phasic coronary inflow in the dog by recording the rate of cooling of a heated wire threaded through an otherwise intact coronary artery The flow pattern was somewhat damped as compared to that recorded by the orifice meter, and no back flow components were present On a theoretical basis alone, the instrument would be incapable of discriminating between forward and backward flow and would be particularly inaccurate at low velocities of flow[4]

In 1928 Broemser[6] developed an optical velocity recorder (tachograph) based on the principle of the Pitot tube and in 1930 Hochrein *et al*[30] used it to record velocity curves in the coronary arteries These velocity curves are quite similar to some obtained by more refined methods at a later date

Phasic changes in coronary inflow were next determined by noting the movement of a foreign substance inserted into the coronary artery stream and in which the coronary artery was perfused by the normally pulsating aortic pressure Stehle (1932) utilizing the Langendorff type of coronary perfusion measured phasic inflow by photographing the movement of a globule of colored toluene placed in the coronary inflow tube as it was carried along in front of a photokymograph[50] Obviously this apparatus had considerable lag Anrep, Davis and Volhard[2] in 1931 adopted the expedient

of photographing the movement of a mercury drop placed in the blood stream just before it entered the coronary artery under a pulsatile pressure head. Despite a considerable lag such an apparatus gives a fair picture of inflow at a coronary orifice.

In 1935 phasic changes in coronary inflow were predicted by the so-called differential pressure method.[18, 28] Since consecutive changes in flow are the resultant of differences in pressure which exist from moment to moment in the peripheral and central end of a coronary ramus, and since the pressure variations in the central end closely follow those in the aorta,[5] the variations in flow through the vessels of the heart are determined by recording with properly calibrated optical manometers the aortic and peripheral coronary pressures and then enlarging and subtracting these curves. The differential curve thus constructed with zero pressure as a base line represents the rate of flow at any point, and the areas beneath different sections of the curve are used to compare the relative volume flows during various portions of the heart cycle. Two assumptions are made: that the rate of flow during systole and diastole bears a linear relation to differential pressure, and that the capacity of the available vascular bed during systole and diastole is unchanged. More recently, with the aid of the rotameter,[1, 2, 16] orifice meter[16] and constant pressure meter,[22] researches have demonstrated that these assumptions are not justified and that such a method may not indicate the directional shifts in flow. In other instances directional changes may be correctly indicated but the magnitude of the flow change is not even remotely represented. While such a procedure has added to our knowledge of the determinants of coronary inflow it must be discarded as an index of coronary flow.

In 1933 Wiggers and Cotton[33] devised a flow meter in which a branch of a coronary artery in the open-chest dog was perfused with Locke's solution from a small reservoir connected to a large chamber filled with air and under a slowly declining pressure. The flow was measured by recording with a very sensitive optical manometer the small pressure drop in the air chamber as fluid entered the coronary artery. The slope of the declining pressure curve gave rate of flow and the total drop over a period of time represented total inflow. Its limitations were a rather low frequency, inability to measure flow under its natural head of pressure, and failure of maintenance of contractions in the area fed by the oxygenated Locke's solution. To obtain more nearly natural conditions the apparatus was improved by Gregg (1934) by using the animal's own blood as the coronary perfusate and by autoperfusing the coronary artery with blood from its own aorta between measurements of coronary flow.

The modern era in the quantitation of phasic flow may be said to have started with the development and refinement of differential and constant pressure flow meters for application to the coronary arteries of the dog with the heart beating *in situ*. Most of our present day concepts regarding phasic flow have come from the use of these methods, consideration of which follows.

In 1940, Gregg and Green[73] described a recording orifice meter for registering phasic coronary inflow. Of the phasic flow meters the orifice meter[3,47] has perhaps been most highly developed and extensively used to measure phasic flow in peripheral vessels as well as in the coronary circulation. It has the advantage over the other devices that the sensitivity can be widely altered without interrupting flow. It was applied to the study of coronary inflow with the hope that by an analysis of part or all of the flow pattern, the effect *upon blood flow caused by cyclic changes in intravascular volume* associated with volume elastic changes and extravascular compression could be separated from the effect of intrinsic vasomotor changes in the coronary vessels. As will be indicated later, this has been only partially realized.

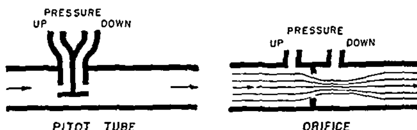
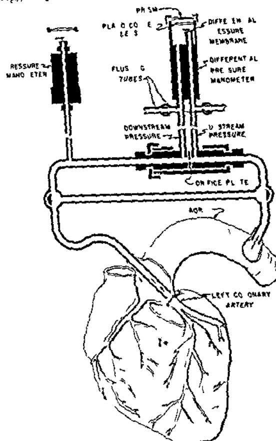


FIG. 20.—Schematic drawings illustrating the principle of the Pitot tube and orifice meter.

The orifice meter makes use of the velocity with which fluid is flowing. In this method the lateral pressure difference is determined *between two regions above and below, respectively, a region of* constriction (the orifice) in a flowing stream, the cross sectional area of which is maintained constant. Because of the higher stream velocity below the constriction, the downstream lateral pressure (Fig. 20) is lower, but most of the pressure difference due to the induced change of velocity is regained. The pressure difference which is proportional to the flow may be optically recorded by a differential manometer. The device can be used for phasic flow irrespective of directional changes in flow. However, its use (as with all devices inserted into a vessel) introduces some reduction of the lumen of the coronary vessel and causes a considerable pressure drop. Hence it should not be used for determining coronary venous flow.

In use the orifice meter (or Pitot tube or venturimeter) is inserted into a coronary artery as illustrated (Fig 21) and attached to a differential pressure manometer which is mounted in the carriage of a pressure manometer (See Fig 13 p 41 for details) The manometer is a rubber membrane optical pressure manometer such as used by Gregg for pressure recording except that the rubber is very



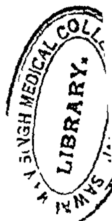


Fig 21 —Diagram of orifice meter differential manometer and connection for measuring coronary inflow Cannula inserted through brachiocephalic artery into aorta and tied in left coronary ostium Details in text

thin and a chamber filled with saline surrounds the front surface of the membrane for the application of counter or downstream pressure The chamber is closed by a plano lens in front of which is an adjustable prism of suitable power to correct the color separation in the recording beam which occurs as the result of its transmission through fluid The upstream pressure is applied to the inner side of the

membrane, the downstream pressure to the external surface of the membrane. More recently, an adjustable orifice[47] has been substituted for the orifice plate of fixed diameter which had to be removed wherever a change in sensitivity was desired (Fig. 22). The *precautions needed to prevent hysteresis and to insure an adequate* frequency already described for pressure manometers apply equally to this phasic recorder. A natural frequency of 50 to 70 cycles/sec is easily attainable and is adequate for determining phasic coronary flow (Fig. 22). The optical projection system already described for use with pulse pressure determinations is used with phasic flow recorders.

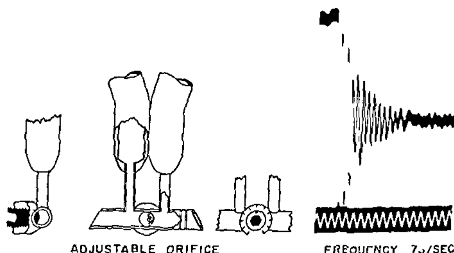


Fig. 22.—Semi-diagrammatic sketch of modified orifice flow meter with readily adjustable orifice. Back, front, and side view of orifice with cut-away sections showing relations of internal parts. On right, typical frequency, 70 cycles per second obtained with adjustable orifice meter. (Gregg and Shipley.[47])

In 1937 Johnson and Wiggers[31] adapted the differential manometer of Frank[14] employing the principle of Pitot tubes to the *measurement of coronary sinus outflow*. The Pitot tube is basically the same in operation as the orifice meter. In this method the difference in pressure is determined in two tubes inserted into a coronary vessel, one directed upstream, the other downstream. The pressure difference is entirely *a function of the velocity of flow* at the two points (Fig. 20).

A constant pressure meter of improved design was made by Green and Gregg in 1940. A small reservoir filled with blood expands at its upper end into a large chamber filled with air maintained at the prevailing aortic systolic pressure, while its lower end is connected

to a coronary artery (Fig. 23). The chamber is filled with blood between determinations. The flow is measured by attaching to the air chamber a very sensitive optical capsule which registers the slight decline of chamber pressure as blood leaves it and enters the coronary artery. The calibrated slope of the declining pressure curve gives rate of flow and the total drop over a period of time represents total flow.[17,30] Quantitation of coronary venous drainage can be obtained with this device by letting blood flow into it with its con-

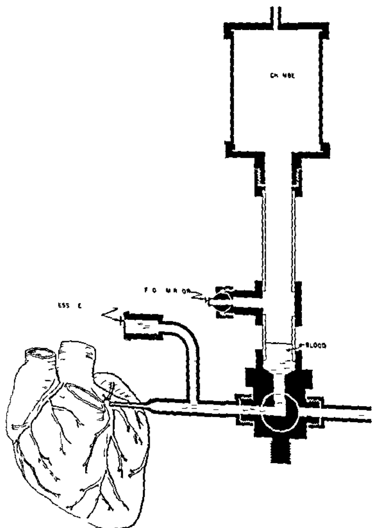


Fig 23 – Diagram of constant pressure flow meter. Discussion in text (Green and Gregg[17])

tained air at atmospheric pressure. Its improvements over previous types of constant pressure flow meters are that it has a higher frequency and records with no appreciable lag.

More recently, the apparatus has been modified by Eckstein[12] to obtain continuous recording of the inflow. Blood continuously enters the chamber at approximately a constant rate by means of a pump attached to a convenient artery, and flow from the chamber to the coronary artery is detected by an orifice meter or rotameter in the circuit (Fig. 24).

Because of the maintenance of a constant perfusion pressure (if attached to the artery), or because of the maintenance of a constant drainage resistance (if attached to the coronary sinus), the use of such perfusion devices permits deductions only with reference to the factors regulating the resistance to coronary inflow or outflow.

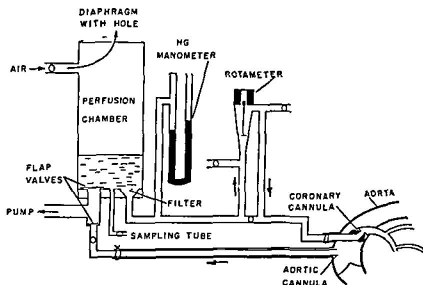


FIG. 24.—Diagram of constant pressure flow meter as used by Eckstein *et al.*[12]

Finally an electromagnetic flow meter[35, 36] has been used to measure phasic rate of flow. This device utilizes the principle that an EMF is induced in the blood stream as it flows through a magnetic field. The apparatus consists of an amplifier, a recording galvanometer, a horseshoe magnet within the poles of which is an insulated sleeve applied to the vessel and containing two non-polarizable electrodes. It has been applied to accessible peripheral vessels but as yet has not been used to measure coronary blood flow, possibly because of the difficulty that might be encountered in avoiding the influence of the cardiac action potentials. Compared to the orifice

meter flow curves the patterns recorded with this instrument are somewhat damped

MEAN FLOW RECORDERS

One of the earliest and simplest methods for determining the mean rate of accumulation of coronary venous blood was the insertion of a Morawitz cannula[39] or its equivalent into the coronary sinus or an anterior cardiac vein and allowing the blood to flow periodically into a graduated chamber or an Archimedes bucket. The volume of flow into the chamber has also been indicated by recording the height of the fluid by a float arranged to write as a sloping line on a kymograph record.[6] As previously indicated the adequacy of this approach for determining left coronary inflow depends on the constancy of the fraction of left coronary inflow draining by this channel.

Similarly mean coronary inflow was early determined by perfusing a coronary artery at systolic (or any desired) pressure at an essentially constant temperature from a calibrated closed perfusion chamber in a manner similar to that described for phasic flow[32] the blood flow being indicated by graduations on the reservoir. The values obtained are correct but as already indicated for this device their interpretation is limited to a consideration of peripheral coronary flow determinants since the perfusion pressure is constant.

Mean flow through the coronary arteries or veins as well as other vessels has been determined by several types of thermostromuhrs which operate on the principle that when a circuit is formed of two wires of different metals and one of their junctions is at a higher temperature than the other an EMF is produced in the circuit. The proper temperature difference is created by a high frequency or direct current. The rate of blood flow is related to the differential temperature of the two junctions.

The first thermostromuhr for measuring mean flow in an unopened vessel was constructed by Rein in 1928.[40] The apparatus consisted of two thermal junctions heated by a diathermy unit supplying a small and constant amount of heat. When mounted in a suitable block and snugly applied to an artery a part of the heat is carried away by the blood hence the rate of cooling of the thermal element depends upon the rate of blood flow.

In 1935 Schmidt and Walker,[41] in 1937 Baldes et al.[3] and in 1945 Bennett[4] each described a direct current stromuhr. In use as a direct current stromuhr a heating element and two thermojunctions are mounted either in a rigid insulating sleeve snugly fitted to an unopened blood vessel[3,4] or in a cannula inserted between the cut

ends of the vessel.[4] The thermojunctions (upstream, or cold) and downstream (or hot) are placed respectively, above and below the heater,[3] or the downstream junction is attached to the heater.[43]

The mechanism by which changes in differential temperature of the thermal junctions reflect changes in flow has been only partially elucidated. In the type of thermostromuhr (Fig 25) in which the

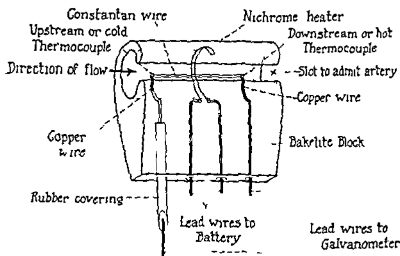


Fig 25 —Diagram of direct current thermostromuhr

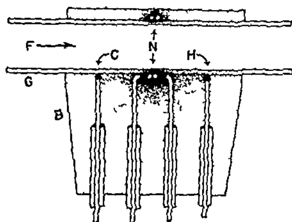


Fig 26 —Diagram of concept of gross heat distribution within a thin sagittal section of direct current thermostromuhr. Density of stipling indicates relative temperature elevation. *F* fluid, *G* glass tube, *B* bakelite block, *C* cold junction, *H* hot junction, *N*, heater. (Gregg *et al* [4])

cold and hot junctions are mounted with the heater in the same insulating block,[3] both junctions are heated by the heater largely through the block and are hotter than the passing fluid; hence the differential temperature of the two junctions is determined by the

respective rates at which they are cooled by the passing fluid[43] (Fig 26) In types in which the cold junction is mounted separately from the hot junction and heater[43] the cold junction and the incoming fluid are presumably more nearly of the same temperature and the hot junction records all or a constant proportion of the temperature rise sustained by the fluid as it passes the heater In either instance since the cross section of the vessel is held constant the volume of flow is related to the differential temperature of the two junctions provided environmental factors do not alter this relationship However Schmidt and Hendrix[44] first suspected that the direct current thermostromuhr was subject *to a number of* possible sources of error and subsequent tests *in vivo* and *in vitro* have revealed serious deficiencies in the application of this thermal principle to the measurement of blood flow[4, 7, 45] Several external and internal environmental factors other than rate of blood flow influence significantly and unpredictably the empirical flow readings by altering the relative rates of heat loss to the environment at the two junctions or the heat distribution between the two junctions These limiting factors include the artery used angulation of the unit with respect to the artery movement of intra and extravascular fluid near the unit lack of linearity between the temperature changes within the unit and blood flow changes in blood temperature uneven temperature in various parts of the blood stream viscosity of the metered fluid and finally the presence of periods of zero flow or retrograde flow (back flow) in the flow pattern

The back flow effect is particularly important since the flow pattern in most arteries either normally contains back flow or it can be induced and the instrument is highly sensitive to the presence of even small amounts of back flow in the pattern This back flow effect on the apparent flow as indicated by the thermostromuhr is illustrated in the curves of figure 27 which has been assembled from actual records and data obtained in different experiments The curves represent the changes in phasic flow back flow and mean blood flow that occurred in the femoral artery of an anesthetized dog during local elevation and *decline of* venous pressure by application of a tourniquet and its subsequent release The flow was recorded simultaneously by the orifice meter rotameter and thermostromuhr It will be observed that with this procedure flow as indicated with the orifice meter and rotameter first decreases and then increases It will also be observed that a back flow component is present in the control period is maximal during the period of greatest reduction in flow and is largely or entirely absent during the early phase of recovery (following tourniquet release) when the flow

is considerably increased. Under this condition in which the blood flow decreases and the back flow component simultaneously increases in magnitude the net effect on the thermostromuhr is a decrease in temperature gradient between the two thermocouples so that the instrument erroneously indicates an apparent increase instead of an actual decrease in blood flow. Similarly, following tourniquet release, the actual increase in blood flow which is sufficient to eliminate the back flow component from the flow cycle, is recorded as an apparent decrease in blood flow by the thermostromuhr. Thus

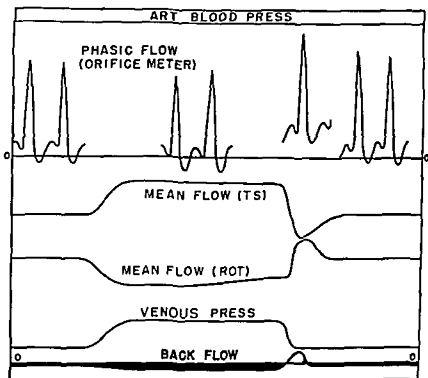


FIG. 27.—Schematic drawing to illustrate the dynamic change in the vessels of the extremities which are responsible for failure of the thermostromuhr to indicate correctly flow changes during local venous occlusion and release. Back flow, black area; 0, zero flow. Details in text. (Gregg *et al.*[23])

the magnitude of the effect of a small increase or decrease *in back* flow indicated by the thermostromuhr as an increase and decrease in flow, respectively, may be greater than the effect of an actual large decrease or increase in flow and the instrument will fail to indicate directional changes in flow. It is hoped that ways and means will be found eventually to eliminate this, as well as other errors inherent in the method since it can be used in unanesthetized animals

Comparable *in vivo* and *in vitro* tests of the high frequency thermostromuhr designed by Rein[40] have not been made *In vitro* studies of the two types of the thermostromuhr under the same conditions indicate that the direct current thermostromuhr compares unfavorably with the high frequency thermostromuhr[8]

While of these older methods the use of the constant pressure meter for inflow and a Morawitz cannula or its equivalent for outflow has added to our store of knowledge the results have suffered from the fact that with these devices it has not been possible to measure flow (*1*) continuously (*2*) with a normally pulsating aortic pressure and (*3*) with the animal in the unanesthetized state Recent development of the rotameter has obviated the first and second objections while the nitrous oxide method permits discontinuous observations in the normal state

In 1934 Soskin[49] measured mean rate of blood flow by timing visually the passage of an inserted air bubble through a glass tube of known length and volume which had been placed between the cut ends of the vessel through which the flow was measured (Fig 28)

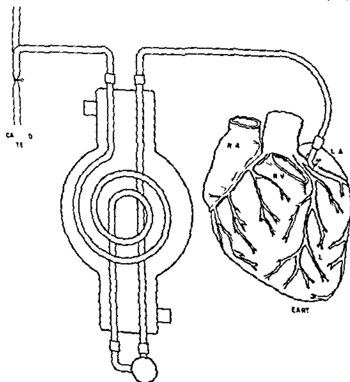


Fig 28 —Diagram of typical bubble flow meter (Bruner)

The method has been improved [7,10] and used to measure coronary inflow, and more recently, the bubble has been timed photoelectrically [44]. Because of the resistance to flow from the long (approximately 1 meter) tube used, the device should not be used in the coronary veins.

The rotameter was originally developed commercially [13] for measurements of fluid flow, but it was not until 1942 that it was adapted to the quantitation of blood flow by the author [29]. The device has been extensively used to record mean rate of flow in the coronary arteries, coronary veins and peripheral vessels and also to determine cardiac output and input [4]. It is probably the best method for continuous and accurate quantitation of mean coronary blood flow with the heart beating *in situ*.

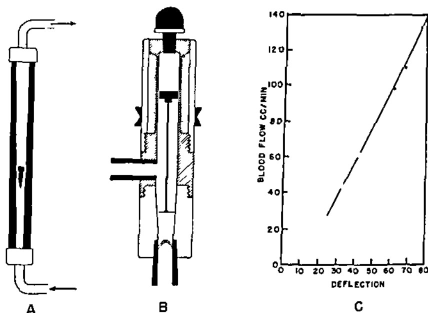


Fig. 29.—Schematic drawings of (*A*) visual reading rotameter with plumb bob shaped float. (*B*) rotameter with type of float minimally affected by viscosity. (*C*) typical calibration curve with Type B rotameter.

Two types of rotameters together with a calibration curve are illustrated in figure 29 A, B. Basically, the device consists of a vertical transparent tube with tapered bore within which the height of a float is determined by the rate of flow. With upward flow through the tube, the float is lifted until it reaches a height determined by a balance of the downward force (weight of float minus weight of displaced fluid), and the upward force (pressure drop across the float times maximal cross sectional area of float). As flow increases the

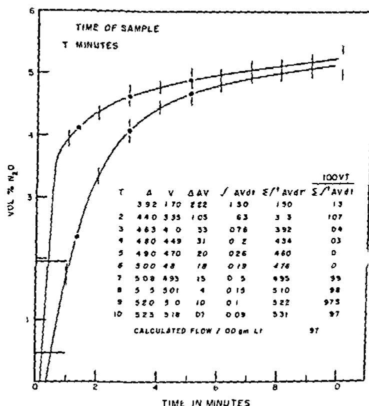
balance is altered and the float rises to a new position at which the increase in the annular orifice is large enough to reduce the pressure drop across the float to that existing at the previous flow level When the plumb bob-shaped float in figure 29 is used changes in blood viscosity affect considerably the calibration curve This effect may be almost entirely eliminated by use of a float similar to that described by Fisher *et al* [13] in which the major part of the float is removed from the flowing stream with high velocity to a stagnant region of zero velocity (Fig 29 *B*) With the latter procedure the calibration is essentially linear (Fig 29 *C*) The position of the float may be read visually [9] or for continuous optical recording of flow a modified rotameter is used in which changes in the vertical position of the float are detected by an induction mechanism which is connected to an optically recording galvanometer [45] The rotameter quantitates flow with an error of about ±5 per cent

More recently the nitrous oxide method has been used to measure blood flow The method first utilized for measuring cerebral flow [34] in 1945 and later left coronary inflow [11, 14] in 1948 is based on the Fick principle, i e the blood flow per unit of time through an organ is equal to the amount of a substance taken up by that organ in a given time divided by the difference in concentration of the substance in the arterial blood supply and venous drainage of the organ *in the same time period* In the nitrous oxide method left coronary inflow is determined by dividing the nitrous oxide uptake of the heart by its A V difference in the coronary system The denominator in the Fick equation is found by computing the integrated difference between the concentrations of nitrous oxide in arterial and venous blood during the period of equilibration with a low concentration of nitrous oxide The concentration of gas in the tissue at the time of equilibrium (the numerator in the Fick equation) is unobtainable directly in the intact animal or man and is assumed to be equal to the product of the venous concentration of the gas (after equilibrium is established) and a partition coefficient (unity in the case of the heart[35]) When the equation is multiplied by 100 units for blood flow are obtained which in the case of the heart are expressed as cc of blood flow per minute per 100 gm of myocardium

In use in the heart several simultaneous arterial (any artery) and venous (coronary sinus by catheter) blood samples are drawn in lightly anesthetized or unanesthetized dogs from the beginning of nitrous oxide inhalation to the time of its equilibrium or during denitrogenation [5] Large dogs (20 kilograms or more) and large blood withdrawals (20 to 60 cc) are necessary However the employment of this procedure largely obviates the criticism of other methods

by utilization of the animal in a state more nearly approximating the normal. An example of left coronary blood flow determination by this method is in figure 30.

Originally, satisfactory agreement was found between left coronary blood flow values obtained with the nitrous oxide method and values obtained simultaneously by direct measurements made with the bubble flow meter[11] in a major branch of the left coronary artery in the open chest dog. For the bubble flow meter, the flow in cc./100



T	A	V	Δ AV	∫ AVdt	Σ∫ᵗ AVdt	100VT / Σ∫ᵗ AVdt
	3 92	1 70	2 22	1 30	1 50	1 3
2	4 40	3 35	1 05	63	3 3	107
3	4 63	4 0	53	0 76	3 92	04
4	4 80	4 49	31	0 2	4 34	03
5	4 90	4 70	20	0 26	4 60	0
6	5 00	4 8	18	0 19	4 76	[illegible]
7	5 08	4 93	15	0 5	4 95	99
8	5 5	5 01	4	0 15	5 10	98
9	5 20	5 0	10	0 1	5 22	975
10	5 23	5 18	07	0 09	5 31	97

CALCULATED FLOW / 00 gm LT [illegible] 97

FIG. 30.—Graph indicating typical nitrous oxide saturation curves obtained in determining coronary flow/100 gram/left ventricle in an anesthetized open chest dog. Upper curve from carotid artery, lower curve from coronary sinus by catheter. Discussion in text.

gm. of left ventricle was determined by dividing the measured flow by the quantity of heart tissue stained when Evans Blue dye was injected into the cannulated coronary artery and the coronary venous blood was obtained by a cannula tied into the great cardiac vein. Flow measurements have not been reported before and after induction of anesthesia *to determine the effect of the nitrous oxide per se* on the vasomotor state of the coronary bed. Because of its great importance, the necessity for confirmation of the adequacy of the method is apparent. The nitrous oxide method is now being evalu

ated in the author's laboratory [18] (1) when the venous blood samples for the nitrous oxide procedure are withdrawn from an intravenous catheter introduced from within the venous system and lying freely in the coronary sinus and (2) by comparing it with simultaneous direct measurements of *total* left coronary artery inflow continuously recorded with an optically recording rotameter [4] To date the measurements show a considerable difference between left coronary in flow as measured by the two methods The reason for the difference has not been established

The individual advantages and disadvantages of the mean and phasic flow devices have been largely considered with each method However certain blanket criticisms apply to all All the methods limit flow to a variable extent and those devices which require insertion into a coronary vessel of an anesthetized and operated dog to which an anticoagulant has been given have the additional disadvantage of inducing a variable and unknown degree of insult to the cardiovascular system and its associated nervous and metabolic mechanism hence the interpretation of the experimental results in terms of occurrences within the normal animal is necessarily restricted

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Chapter 5

DISTRIBUTION OF CORONARY BLOOD FLOW PHASIC FLOW CURVES

DISTRIBUTION OF CORONARY ARTERIAL INFLOW

In the anesthetized dog in which the left and right coronary inflow were simultaneously quantitated with the rotameter, the left coronary flow approximated 85 per cent and right coronary flow 15 per cent of the total coronary inflow.[4] The arrows in figure 31

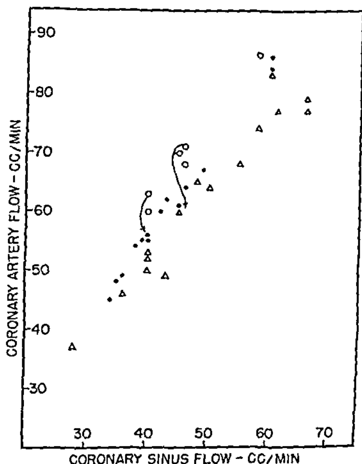


Fig. 31 —Graph showing relationship of common left coronary inflow or total coronary inflow (ordinate) and coronary sinus outflow (abscissa) under different dynamic conditions. Dots and triangle: common left coronary inflow in 2 experiments. Circles: total coronary inflow (right and left). Dots at end of arrows: common left coronary inflow after clamping right coronary artery. (Gregg *et al.*[21])

illustrate the results of a typical experiment A similar distribution exists in the heart lung preparation with the coronary arteries perfused at a constant pressure [4] and in the perfused fibrillating heart [5] This general preponderance of left coronary flow in the dog may apply in man in the small percentage of those hearts which are left coronary artery preponderant but not in most human hearts in which the coronary systems are balanced or the right coronary artery is preponderant [28]

DISTRIBUTION OF CORONARY OUTFLOW

As already indicated the blood which enters the coronary arteries can return to the ventricular cavities by two main routes into the right atrium by way of the coronary sinus and the anterior cardiac veins and directly into the ventricular cavities through the Thebesian veins and the arterio-luminal and sinusoidal vessel

Venous Drainage into the Coronary Sinus —Direct measurement of coronary venous outflow in the isolated heart heart lung preparation and with the heart beating *in situ* has shown that practically all the blood in the coronary sinus arises in the coronary arteries and that the coronary sinus and associated superficial veins emptying near its mouth constitute the major venous drainage system of the left coronary artery [4] With the heart beating *in situ* temporary clamping of the left coronary artery at its ostium immediately reduces coronary sinus flow to values approximating 2 to 3 cc per minute or 5 to 7 5 per cent of the original flow values (12 determinations in 4 experiments see Table 2 expts 1 9) In 3 additional experiments temporary occlusion of the right coronary artery alone reduced coronary sinus flow by a detectable amount in only 2 of 11 determinations (Table 2 expts 7 11) and even when right ventricular pressure was previously considerably elevated by mechanic[al] constriction of the pulmonary artery right coronary artery occlusion did not reduce coronary sinus flow (Table 2 expt 3) However when temporary occlusion of the right coronary artery was superimposed on an existing left coronary artery occlusion (3 experiments 5 determinations see Table 2 expt 10) the coronary sinus flow dropped slightly more by falling further from 2 0 2 5 2 5 3 0 and 3 0 to 1 0 1 0 1 0 1 0 and 1 5 cc thus indicating that possibly 1 t[o] 2 cc of blood was entering the coronary sinus from the right coronar[y] artery under the favorable conditions imposed by left coronary ar[-] tery occlusion (Table 2 expt 10) This small drainage of the righ[t] coronary artery into the coronary sinus is somewhat less than th[at] reported by others using the heart lung preparation [2] The resi[d-] ual and just detectable coronary sinus flow remaining [...]

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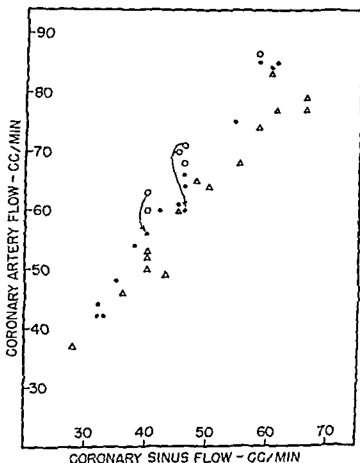


Fig 31 —Graph showing relationship of common left coronary inflow or total coronary inflow (ordinate) and coronary sinus outflow (abscissa) under different dynamic conditions Dots and triangles common left coronary inflow in 2 experiments Circles total coronary inflow (right and left) *Dots at end of arrows common left coronary inflow after clamping* right coronary artery (Gregg *et al* [21])

T a T D T I R F BI OD NTIE C R N K VEN D N E T E R

Exp No	Aortic Pressure Before mm Hg	Aortic Pressure During mm Hg	Arterial Inflow Before	Arterial Inflow During	Outflow Before	Outflow During	Retrograde Inflow/Outflow Before	Retrograde Inflow/Outflow During	Remarks
			L ft C		(Coronary S)				
1	[illegible]	85			55 0	0			Eff ct of l n pi g l ft co onary a t ry c o ona y nus flow
	85	5			0	1 0			I ffect of cl mp ng rigl t a l l ft c nary arter e on o o ry s nus flow
3	8	8	40	4	1	3	8	9	I ff t of clamp g rigl t coro a y arte y on or s t u flow f llowi g ul art c u ctn
4	0	(	40	60	36	4	3	−0	Eff t of p lmo a y rt c tr ction (4 m) with p rti l a rt l od pr sure n pen at o
5	90	5	[illegible]	54	40	4	−3	8	I ff t of low p o ta eous fall in t e l lood pr u e (l min)
6	55	55	(	55	43	60	( )	1	I j of 0 1 c Tl ean n i l ft co a ery
			Rt & Left C		(Co S n u)				
	10	60	1	60	46	40	( )	-	I ff t of l amp ng r gl t n ry art ry or co onary n s flow
8	0	-	60	56	40	58	60	67	I ffe t of p lmonary art c n trict o (7 m n) with a rtic l lood pres u e ompen at o
			Right Co		Cor Sinus				
1	105	105	11 0	15 0	63 0	3 0			I ffect of cla np ng commo left c r art on co onary s s flo
10	105	105	15 0	0	3 0	1 5			Rigl t c ronary art ry lamp l aft r p evio s clan p g of l ft co ary artery
1	68	68	14 5	0	34 0	30 0			I ffect of clan p ng rigl t o onary artery on c on ry s nus flow Ma im m effect
			Right C		AC V				
	0	−0	-	19	- 0	13 0			Puln nary art co trict o AC vei flow Flow mea ured in 1 of 3 major AC e n Approx 50% of AC flow fr m right coronary arte y
3	90	92		11 5	5 0	11 0			Pulmonary artery con tri t o Flow m asured in 1 of 3 ma jor AC v i s Appr x 70% of AC flow fr m right cor n ary artery

truly complete acute coronary artery occlusion (*See also* expt 2) presumably arose from small twigs of the coronary arteries which were always found (by post mortem injection and inspection) to be central to the sites of coronary artery occlusion

Although essentially all blood in the coronary sinus appears to arise from the left coronary artery not all the left coronary artery inflow leaves by this channel Measurements with the heart beating *in situ* reveal that in different experiments 64 to 83 per cent of blood from the left coronary artery drains through the coronary sinus (determined by temporary occlusion of the right coronary artery) Some of the values are in Table 2 experiments 3, 4 5 6, 7 8 under a variety of dynamic conditions These results are in general agreement with previous observations by others using the heart lung and isolated heart preparations [1,35]

Early investigators, using the heart-lung preparation [1,11,35] observed that coronary sinus outflow indicated semi-quantitatively the changes, but not the magnitude of left coronary or total coronary inflow Since simple and accurate methods for quantitating coronary inflow were not then available, measurement of coronary sinus outflow with the heart beating *in situ* has been widely used to indicate quantitative and directional changes in flow More recent investigators[30,31,36,4] have challenged the general application of this relationship on the basis of experiments performed with the heart lung preparation isolated heart fibrillating heart, perfused dead heart and heart beating *in situ* From a practical standpoint the issue would seem of little import since there are now available simple and adequate methods of directly measuring coronary inflow in a somewhat more reliable preparation However in view of the rather unnatural preparations which were generally used the abnormal pressure relations created in some of the experiments and because in some instances the deductions were made on the basis of indirect evidence it was of interest to repeat certain experiments under conditions in which the normal physiological state of the heart was less disturbed With the dog heart beating *in situ* and with rotameters to measure coronary inflow and coronary sinus outflow the effects of various procedures were determined Changing aortic blood pressure, elevation of right ventricular pressure saline and blood infusion and the intracoronary arterial injection of drugs did not greatly alter the relationship of coronary sinus outflow to left coronary inflow, *and in no instance would a significant change in left or total coronary inflow have been incorrectly indicated by the corresponding coronary sinus outflow* In one experiment the coronary sinus flow was 79 *per cent of left coronary inflow* ($\pm$ 3 8) in another

ship of coronary sinus flow to left coronary artery flow varies in different experiments

The physiological significance of the ingenious heart lung experiments of Katz *et al* [31] is not known in which when the coronary perfusion pressure was lowered and the pressure within the heart cavities was raised the coronary sinus outflow exceeded considerably total coronary inflow A reasonable explanation is that they indicate that retrograde flow through the Thebesians can be made to occur in a heart by creating highly abnormal and unphysiological pressure gradients If significant retrograde flow through the Thebesian vessels were possible within physiological limits the pressure gradients between the ventricular cavities and the coronary vessels should be optimal for its demonstration during a period of complete occlusion of the coronary arteries However as already indicated with hearts beating *in situ* temporary occlusion of both coronary arteries decreases coronary sinus outflow to almost zero within 10 to 20 seconds (Table 2 expts 2 10) no blood flow from the ventricles into the coronary arteries can be demonstrated and the hearts do not survive [144]

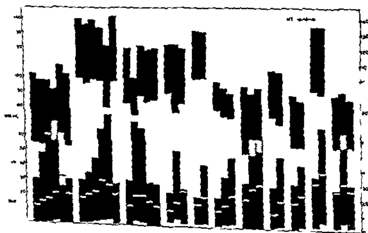


FIG 57 Bar graph showing the effect on coronary inflow of augmentation of right ventricular pressure by pulmonary artery constriction Right right coronary inflow left ramus descendens inflow Abscissa—C control O partial occlusion of pulmonary artery R release of pulmonary constriction numbers time elapsed in minutes following pulmonary artery constriction or release Common ordinate scale denotes all pressures in millimeters of mercury and flow in cubic centimeters per minute Lower solid bars systolic and diastolic right ventricular pressures upper solid bars aortic systolic and diastolic pressures Dotted lines in lower bars denote values of right or left coronary inflow (Gregg *et al* [22])

this value was 73 per cent (± 2.6). Also, in the latter experiment coronary sinus flow equaled 64 to 68 per cent of total coronary inflow. Many of these values are illustrated in figure 31 and Table 2, the data for which were taken from 63 determinations in two experiments.[24]

The observations on this relationship during constriction of the pulmonary artery are of particular interest. Various investigators[30, 31, 36, 45] have stressed the importance of right ventricular pressure in modifying right coronary flow. Primary emphasis is placed upon the reasoning that elevation of right ventricular pressure by increasing the resistance against which the Thebesian vessels may discharge venous blood into the right ventricular cavity, causes a diminished blood supply to the right ventricle. The observed concurrent increase in coronary sinus flow with elevation of right ventricular pressure first observed by Johnson and Wiggers[30] (Table 2, expt. 4), is interpreted to indicate that blood is shunted away from the Thebesians of the right heart into the coronary sinus, or that there is an actual retrograde flow of Thebesian blood from the right ventricle to the veins emptying into the coronary sinus. While such deductions may conceivably apply under hemodynamic conditions artificially induced in certain types of preparations, they do not constitute a logical explanation for the findings obtained under more nearly normal physiological conditions. As already indicated, with the heart beating *in situ*, most of the venous drainage of the right heart is through the anterior cardiac veins rather than through Thebesian channels to the right ventricular cavity.[8] Actually elevation of right ventricular pressure increases both right and left coronary *inflow*,[7] *which fact alone is sufficient to account for the increased coronary sinus outflow* (*See* Fig. 32 and Table 2, expts. 4, 8, 12, 13). For the data in figure 32, the right ventricular systolic pressure was either gradually or abruptly elevated to 80 mm. Hg with or without compensation of the accompanying reduction in aortic blood pressure. This was accompanied by a progressive and *considerable augmentation in right coronary inflow* (25 to 200 per cent) and a smaller increase in left coronary inflow (19 to 29 per cent). In addition, flow through the anterior cardiac veins increased greatly[4] (Table 2, expts. 12, 13).

These results indicate that in any one experiment with reasonably normal hemodynamic conditions prevailing, changes in coronary *sinus flow can probably serve as a directional indicator of left coronary inflow* (and presumably also of total coronary inflow), although the actual volume cannot be accurately predicted since the relation

veins may be greatly augmented by clamping the thoracic aorta or by drug injection

To establish the source from which the anterior cardiac vein flow arises the right and left coronary arteries were both occluded for 25 to 30 seconds The aortic blood pressure fell about 5 to 10 mm Hg during this period In one experiment the flow from the anterior cardiac veins was reduced almost to zero In other experiments a residual flow remained (0 5 to 1 0 cc) equal to 5 to 10 per cent of the control anterior vein cardiac flow Examination of the latter hearts at the end of the experiments revealed the presence of 1 or 2 right coronary artery twigs central to the right coronary cannulae which were not occluded during the experimental procedure Thus almost all if not all the anterior cardiac vein flow must have arisen in the coronary arteries [24]

From their anatomical distribution the anterior cardiac veins would presumably drain myocardial regions supplied by the right coronary artery Simultaneous measurements of right coronary inflow and anterior cardiac vein outflow show that the latter may vary from 72 to 118 per cent of the former and that both vary in the same direction under the influence of altered dynamic states (Table 3) Actually temporary and separate clamping of the right and left coronary arteries shows that both contribute to the anterior cardiac vein flow and as established by such clamping procedures the respective contribution of the two coronary arteries is variable but the major contribution is from the right coronary artery Approximately 50 to 92 per cent of right coronary artery inflow drains into the right atrium by these channels while a somewhat smaller volume of anterior cardiac vein blood is derived from the left coronary artery (Fig 33) The amount of anterior cardiac vein flow (0 to 16 cc per minute) arising from the left coronary artery is sufficient in most instances to account for most of the left coronary inflow which does not appear in the coronary sinus but whether a quantitative relationship exists has not been established experimentally because of the technical difficulty in measuring flow simultaneously in both coronary arteries and in all the superficial venous channels of the heart In addition a very small amount of blood from the right coronary artery drains into the coronary sinus For example in 5 experiments with the dog heart beating *in situ* and with the right coronary artery inflow approximating 15 cc per minute temporary clamping of the right coronary artery alone or after previous clamping of the left coronary artery reduced the coronary sinus flow by 1 5 to 4 cc per minute in 3 tests but was without effect in two experiments [24]

Venous Drainage into the Anterior Cardiac Veins —The functional importance of the anterior cardiac veins has been virtually ignored by investigators Recent work has demonstrated that with the heart beating *in situ*, the coronary venous drainage by the anterior cardiac veins is considerable [4,28] In Table 3 are shown typical

TABLE 3 —COMPARISON OF VOLUME OF BLOOD FLOW IN THE ANTERIOR CARDIAC VEINS AND THE RIGHT CORONARY ARTERY

1	2 Mean Blood Pressure	3 Anterior Cardiac Veins	4 Right Coronary Artery	Per Cent $\frac{AC\ Flow}{Rt\ Cor\ Flow} \times 100$	
kgm	mm Hg	cc/min	cc/min		
21.3	85	12.0	12.0	100	Flow measured in all 3 major AC veins
24.0	90	19.0	21.5	89	Flow measured in all 3 major AC veins
24.0	120	26.5	37.0	72	Flow measured in all 3 major AC veins
19.3	94	16.5	15.0	110	Flow measured in both major AC veins
18.2	82	13.5	26.0	[illegible]	Flow measured in 2 of 4 major AC veins
21.5	70	12.0	12.0	100	Flow measured in 3 of 5 major AC veins
18.3	60	26.0	25.0	104	*Control*—Flow measured in all 5
	86	34.0	30.0	113	major AC veins Constriction of aorta
16.5	70	5.0	6.8	74	*Control*—Flow measured in 1 of 2
	125	10.8	11.0	98	major AC veins Constriction of aorta
19.3	70	12.0	12.0	100	*Control*—Flow measured in both
	105	30.0	25.5	118	major AC veins Epinephrine by jugular vein
16.5	70	5.0	7.0	71	*Control*—Flow measured in 1 of 2 major AC veins
	125	21.0	18.0	117	Epinephrine by jugular vein
	125	35.0	34.0	10[illegible]	Epinephrine by jugular vein
21.3	120	6.0	8.0	75	*Control*—Flow measured in all 3 major AC veins
	110	13.0	20.0	65	Nitroglycerine by jugular vein

values for anterior cardiac vein flow in dogs of different weights and under different dynamic states In some experiments, all the major anterior cardiac veins were cannulated in others the flow in only a part of the total number of larger veins was determined In no instance were attempts made to cannulate the smaller anterior cardiac veins In those experiments in which all the major anterior cardiac veins were cannulated the flow values ranged from 8 5 to 26 5 cc per minute As illustrated the flow values from the anterior cardiac

veins may be greatly augmented by clamping the thoracic aorta or by drug injection.

To establish the source from which the anterior cardiac vein flow arises, the right and left coronary arteries were both occluded for 25 to 30 seconds. The aortic blood pressure fell about 5 to 10 mm Hg during this period. In one experiment the flow from the anterior cardiac veins was reduced almost to zero. In other experiments a residual flow remained (0.5 to 1.0 cc) equal to 5 to 10 per cent of the control anterior vein cardiac flow. Examination of the latter hearts at the end of the experiments revealed the presence of 1 or 2 right coronary artery twigs central to the right coronary cannula which were not occluded during the experimental procedure. Thus almost all, if not all, the anterior cardiac vein flow must have arisen in the coronary arteries.[24]

From their anatomical distribution the anterior cardiac veins would presumably drain myocardial regions supplied by the right coronary artery. Simultaneous measurements of right coronary inflow and anterior cardiac vein outflow show that the latter may vary from 72 to 118 per cent of the former and that both vary in the same direction under the influence of altered dynamic states (Table 3). Actually, temporary and separate clamping of the right and left coronary arteries shows that both contribute to the anterior cardiac vein flow and, as established by such clamping procedures, the respective contributions of the two coronary arteries is variable but the major contribution is from the right coronary artery. Approximately 50 to 95 per cent of right coronary artery inflow drains into the right atrium by these channels, while a somewhat smaller volume of anterior cardiac vein blood is derived from the left coronary artery (Fig. 33). The amount of anterior cardiac vein flow (0 to 16 cc per minute) arising from the left coronary artery is sufficient in most instances to account for most of the left coronary inflow which does not appear in the coronary sinus, but whether a quantitative relationship exists has not been established experimentally because of the technical difficulty in measuring flow simultaneously in both coronary arteries and in all the superficial venous channels of the heart. In addition, a very small amount of blood from the right coronary artery drains into the coronary sinus. For example, in 5 experiments with the dog heart beating *in situ* and with the right coronary artery inflow approximating 15 cc per minute, temporary clamping of the right coronary artery alone or after previous clamping of the left coronary artery reduced the coronary sinus flow by 1.5 to 4 cc per minute in 3 tests but was without effect in two experiments.[24]

No consistent quantitative relationship between anterior cardiac vein flow and right coronary flow can be demonstrated. In 6 experiments (80 determinations) in which all major anterior cardiac veins were cannulated, the ratios of anterior cardiac vein outflow to right coronary inflow under different conditions varied from 0.6 to 0.8, 0.81 to 1.43, 0.3 to 1.0, 0.5 to 0.75, 0.73 to 1.37, and 0.57 to 0.9. Considerable variation in the ratio would be expected since the

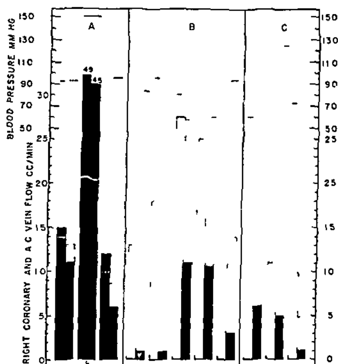


FIG 33.—Chart of data from different experiments illustrating 1) The relative volumes of flow measured simultaneously in the right coronary artery and anterior cardiac veins. 2) The source of the anterior cardiac vein flow as shown by clamping of either the left or right coronary artery. In each part the bar on the left represents the rate of right coronary inflow and that on the right the rate of anterior cardiac vein outflow. Dotted line (and areas) in each pair indicate the control values for both arterial and venous flows. Solid lines (and areas) represent the flow values after clamping of a coronary artery as indicated below. Part A. Flow in right coronary artery versus flow from all major anterior cardiac veins before and during occlusion of left coronary artery. *Epinephrine given intravenously and no control flows obtained before occlusion of left coronary artery. Part B. Flow in right coronary artery versus that from all major anterior cardiac veins before and during occlusion of right coronary artery. Part C. Same as for Part B except that anterior cardiac vein flow was measured from 2 out of 4, 1 out of 2 and 1 out of 4 major AC veins respectively. Transverse dotted lines and bars in upper part of chart, mean aortic blood pressure. Flow (cc per min) in right coronary artery and anterior cardiac veins and mean aortic blood pressure (mm Hg) indicated on ordinate scales. (Gregg et al[2])

anterior cardiac veins drain areas of the heart which are supplied by both right and left coronary arteries Hence a small change in the amount of blood contributed by the left coronary artery can have a relatively large effect on the ratio of total anterior cardiac vein flow to right coronary flow [4]

The percentage of right coronary inflow draining through the superficial veins of the heart is considered minimal since for technical reasons no attempts were made to measure the outflow from the smaller anterior cardiac veins the right auricular veins and many small veins of the right ventricle emptying into the great cardiac vein all of which constitute channels of exit for blood supplied to the right heart by the right coronary artery [5] These findings in the beating heart make completely untenable the conventionally accepted belief that nearly all or even most of the right coronary inflow drains by way of the Thebesians into the right heart Most of the coronary venous blood from each heart appears to drain by way of its own system of superficial veins It follows that the studies of cardiac venous channels flow partitions and Thebesian drainage which have been made in the past without measurement of flow in the anterior cardiac veins should be subjected to a critical re-evaluation before their associated conclusions can be accepted

From the use of heart lung and isolated heart preparations it has been claimed that the Thebesian vessels drain most of the right coronary blood into the right ventricular cavity [28] i e the functioning of the drainage system of the right heart was presumed to be quite different from that of the left heart [27, 28] It is significant that in such studies it was assumed that all coronary venous blood not collected in the coronary sinus and appearing in the right ventricle must have come largely from the Thebesian vessels Katz *et al* [24] reinvestigated the problem by separating the coronary venous drainage into the atria and ventricles by an instrument made to expand in umbrella like fashion at the level of the arteriovenous valves A considerable venous drainage into the right ventricle was again found and regarded as evidence that a significant right ventricular Thebesian drainage occurs—which is an important element in coronary drainage These experiments indicate what can happen in a heart but whether this is what does happen in a normal heart remains to be determined especially since the experiments were done by perfusion of serum-saline mixtures through the coronary vessels of an excised non beating heart and the possible effect of the presence of the instrument upon the outflow from the anterior cardiac veins (the mouths of which open just superior to the ring of the tricuspid valve) was not noted

Luminal Vessels and Their Function.—Histological studies including serial sections, wax reconstructions, dye injections, and perfusion experiments of the isolated heart,[46] have been used to demonstrate the presence and distribution of Thebesian and luminal vessels through which the coronary vessels communicate with the atrial and ventricular chambers of the heart. These channels are much more abundant in the right ventricle. As already indicated, experimental studies with the heart beating *in situ* suggest that these luminal vessels may function in only a limited fashion in the undisturbed, normal heart and, to an extent very much less than previously maintained. Actually, although many experiments have been devised to determine if, when, in which direction and to what extent blood flows through these channels, none has been sufficiently conclusive to justify more than a speculation as to whether they ever function in the normal heart beating *in situ*. The critical objections to most of the experiments can be resolved into either (*1*) the assumption that all coronary venous blood entering the right atrium and right ventricle, exclusive of that which enters from the coronary sinus, has its origin in the Thebesian vessels, thereby ignoring the considerable venous flow from the anterior cardiac veins, and/or (*2*) the establishment by artificial manipulation of decidedly abnormal pressure gradients between the coronary vessels and chambers of the heart for the purpose of demonstrating what are implied to be the normal physiological magnitude and directional changes in Thebesian flow.

NORMAL CORONARY BLOOD FLOW

Left coronary inflow has been quantitated in the human subject with the nitrous oxide method [4] and in the open or closed-chest dog in good condition and with a good blood pressure, by the rotameter [10,19,3,4,5,27,40] bubble flow meter [7,9] nitrous oxide method,[3,1] and by measurement of coronary sinus flow,[9] and in the unanesthetized dog by the nitrous oxide method.[43] The range of values is indicated in Table 4. The highest values (151 cc./100 gm. left ventricle/min.) have been obtained in the unanesthetized dog; curiously, flow values in the normal human are in the same range as in the anesthetized dog, but both are considerably lower (65 to 100 cc./100 gm. left ventricle/min.) than in the unanesthetized dog. No figures are available for right coronary inflow in relation to the weight of the right ventricle. Total coronary flow values ranging from 50 to 100 cc./100 gm. heart/min. have been obtained (*1*) in the isolated, denervated heart whose coronaries were fed by a second

heart and whose work output was small[2] (2) in the heart lung preparation by measuring coronary sinus outflow (3) in the revived human heart perfused at constant pressure[23] It deserves comment that the flow values do not differ more widely in lieu of the great diversity of methods techniques and procedures and the fact that

TABLE 4 —VALUES FOR LEFT CORONARY INFLOW WITH DIFFERENT METHODS IN VARIOUS PREPARATIONS

Author	Left Co Inflow cc min 100 gm Left Vent	Mean Blood Pressure mm Hg	Remarks
Gregg et al	74	80	Anesthetized open-chest dog Flow by rotameter in left coronary artery
Gregg et al	81	80	Anesthetized open-chest dog Nitrous oxide method
Eckenhoff et al	74	133	Anesthetized dog Nitrous oxide method
Goodale et al	1	135	Anesthetized dog Nitrous oxide method
Harrison et al	64	118	Morphinized dog Coronary sinus flow x factor
Spencer et al	151	119	Unanesthetized dog Nitrous oxide method
Bing et al	65	9?	Normal human Nitrous oxide method

in the latter procedure the heart is entirely removed from its normal nervous and humoral control and pressure relations At present these values should be conservatively considered and no emphasis should be placed on any of them as approximating the normal figure They should serve only as reference points in experiments Maximal flow values have never been determined in the anesthetized dog Values approximating 300 to 400 cc /100 gm left ventricle/min have been obtained following epinephrine injection

Flow in the left anterior auricular artery of the heart lung preparation (15 kilo dogs) ranges from 0 08 cc to 0 581 cc per cycle[4] If the heart rate does not exceed 100 per minute this would give very large flows (8 to 58 cc per minute) to the left auricle

The fraction of total cardiac output passing through the coronary arteries varies inversely with the cardiac output Generally this is considered to constitute about 4 to 5 per cent of cardiac output although with rather low outputs (500 cc per min) as much as 9 per cent of cardiac output may flow through the arteries of the heart[7] With quite high cardiac output such as induced by epinephrine injection the coronary flow can be 12 to 13 per cent of the total blood flow[25]

PHASIC FLOW

Of the available methods for measuring coronary blood flow few give detailed information concerning the mechanisms which con

trol it, because such studies involve certain difficulties not encountered elsewhere in similar investigations upon the blood supply to other organs of the body The myocardial wall of the left ventricle not only furnishes the pressure head for driving blood into the coronary arteries, but also offers phasic resistance to coronary flow by its muscular contraction around the vascular bed Similarly the right ventricle creates a rapidly changing resistance to flow in its vascular bed at the same time that the left ventricular contraction presents blood to it under a pulsatile pressure head Since the pressure source for and the resistance to, coronary flow have a common origin, the measurement of phasic flow is the only method that can permit evaluation of the determinants of coronary flow during successive moments of the cardiac cycle

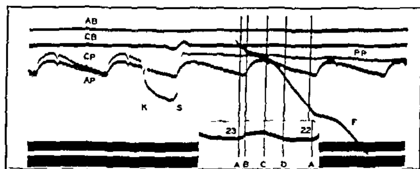


FIG 34 – Reproduction of original record showing phasic inflow into ramus descendens anterior as obtained with the constant pressure meter AP, aortic pressure CP central coronary pressure PP perfusing pressure F phasic volume flow lowest curve is the peripheral coronary pressure obtained a few heartbeats later A B C D vertical intercepts at onset of isometric contraction opening of aortic valves onset of protodiastole and onset of diastasis respectively At K S stopcock turned to give constant infusion

Phasic flow and its determinants have been studied by the methods of differential pressure[17, 6] by the Pitot tube[30] by the constant pressure flow meter,[14] and by the orifice meter[15, 1] As already indicated the results with the first method are not reliable

With the constant pressure meter flow measurements are necessarily made with the central coronary pressure maintained constant This method does not evaluate the effect of pulsations of the central coronary pressure and hence deductions can only be made as to the factors determining the peripheral resistance to flow Examination of the various typical curves obtained in the left or right coronary artery shows that although during systole coronary inflow is reduced a definite forward flow exists throughout the cardiac cycle

In figure 34, in which the circumflex branch of the left coronary artery was perfused at essentially aortic systolic pressure starting at point S, the rate of flow begins to diminish during systole at A (i.e., at the beginning of the isometric contraction period), decelerates further to B (opening of aortic valves) and then remains relatively constant from B to C (start of protodiastole). During diastole the rate of flow starts to increase at C (coincident with the decline of peripheral coronary pressure curve) and reaches a maximum at D (i.e., at about the diastolic valley of the peripheral coronary pressure curve). For the remainder of diastole the rate of flow is essentially constant. Reflection indicates that, since to obtain these flow curves the coronary arteries were perfused at a relatively constant pressure, the points of inflection of the curves should mirror the successive changes in peripheral coronary resistance to flow. Actually, examination of the peripheral coronary pressure in figure 34, obtained by abruptly clamping the coronary artery a few heart beats later in the same experiment and recording the pressure in the artery distal to the point of occlusion until equilibrium occurred (8 to 10 cycles), shows that this is the case.

Although such curves indicate that left ventricular contraction reduces systolic flow at definite time intervals, the question of the magnitude of such flow reductions is not so easily answered. Usually, the flow is not completely *arrested in systole*, i.e., never reaches a zero slope when the perfusion pressure approximates the aortic systolic pressure. However, in different dynamic states and with certain drugs there may be a systolic flow point of zero velocity, or the systolic flow may not be greatly reduced as compared with the diastolic.[70]

These flow patterns have been recorded with the orifice meter in the coronary arteries and most peripheral arteries of the locally or generally anesthetized dog under a great variety of dynamic states.

Flow patterns (and simultaneous intra-arterial pressure curves) characteristic for the peripheral arteries are illustrated in figure 35. For clearer visualization of the flow rate/time relationship in a given curve and to permit comparisons among different curves, the recorded patterns have been rectified and redrawn to a linear ordinate scale. Examination of a large number of such recorded flow curves has made possible the identification of certain distinguishing characteristics.[37, 41] A flow pattern is made up of waves whose directional changes have a qualitative correspondence with gradient changes in the simultaneously recorded intravascular pressure pulse and which may be characteristically distinctive for that artery and bed. Since flow velocity varies with the differential pressure existing at the site

of the flow meter similarity in contour of the flow and applied pressure pulse should be one criterion for the comparison of flow curves from different arteries. Certain patterns, especially those of the *superior mesenteric and renal arteries, have a rather well rounded* and sustained systolic portion in relative conformity to that of the pressure pulse. Those of the hepatic and common carotid arteries are less well rounded, those of the brachial and femoral arteries have a sharp systolic peak. The pulse pressure is seen to be small in the case of the renal and axillary patterns, somewhat larger in the superior mesenteric and hepatic, while that of the common carotid, and particularly the femoral pattern, is quite large. Back flow components have been consistently found *in the femoral and axillary* patterns and are frequently found in the common carotid patterns,

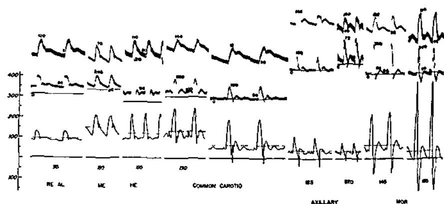


FIG 35.—Reproduction of original pressure (upper) curves and flow (middle) curves as recorded in the various arteries indicated. Lowest curves, rectified reconstructions of original velocity curves. Pressure values (mm Hg) and flow rates (cc per min) indicated as numbers on respective curves. Horizontal lines with 0 zero flow. Heart rate numbers at bottom of each segment. Dotted lines mean flow for each segment to which ordinate scale (flow in cc per min) applies. (Shipley, Gregg and Schroeder [41])

while the renal, hepatic, and superior mesenteric flow curves have exhibited only forward flow. However the main feature which permits a separation of the curves is the variability of the early diastolic rate of flow with respect to the presystolic rate. Comparison of this relationship with that of the corresponding early diastolic and presystolic points on the pressure curve shows that the superior mesenteric, renal, hepatic, common carotid, axillary, and femoral patterns have, on this basis, a progressively graded dissimilarity to their respective pressure curves.

Inflow patterns for the coronary arteries are depicted in figure 36. In hearts in good *condition the flow curve in the right* coronary is

generally patterned after the aortic pressure pulse or central coronary pressure curve while that in the left coronary artery (and at times in the right coronary) shows no similarity to its corresponding pressure curve Back flow is almost always present in early systole in the left coronary artery flow pattern but this is infrequent in the right coronary and when present its time of appearance is roughly comparable to that for the peripheral arteries i e in late systole or early diastole

Thus flow patterns in heteronymous arteries are found to exhibit wide variations in magnitude timing direction and rate of flow and in similarity of contours to their respective pressure pulses

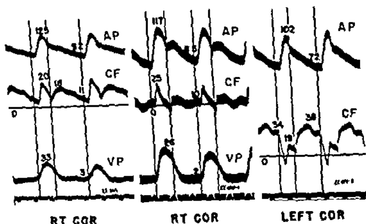


Fig 36 — Reproduction of original *aortic pressure* (AP) curves coronary flow (CF) curves and right ventricular *pressure* (VP) curves Numbers on *curves* pressures (mm Hg) and flow rates (cc per min) O *zero flow* Time 0 2 sec

For the peripheral flow patterns in figure 35 a method of analysis and interpretation has been developed by means of which the probable determinants of and interrelated influences upon phasic rate of flow can be quantitatively evaluated [37 41] This is considered in some detail for its understanding lays the groundwork for the consideration of the problem of the more complex coronary patterns In figure 37 is shown a rectified reconstruction of an arterial flow pattern and pressure curve from the femoral artery Such a flow curve is a record of the direction and velocity with which blood flows by a point in an artery supplying a given vascular bed Under conditions of reasonable constancy the mean rate of arterial inflow during a cardiac cycle is equivalent to the existing mean rate of blood flow through the bed (line M M) The areas representing volume flow which lie above (B E) and below (A C D F) the mean

flow line are equal by virtue of the mean position of the mean flow line (M M) Since the femoral venous flow pattern has been found to be essentially a smooth "linear" flow curve corresponding very closely to the mean flow (line M M), it follows that from the point of recording arterial inflow to that of recording venous outflow the flow pattern has been smoothed out presumably by viscous resistance to flow and volume elastic moderation Thus the relationship of the pulsatile arterial inflow curve to its corresponding almost linear venous outflow curve should indicate the essential mechanism

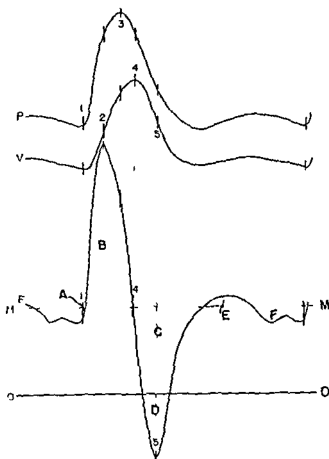


Fig 37 —Upper curve P reproduction of femoral arterial pressure pulse Middle curve V derived intravascular volume curve Lower curve F reconstructed flow pattern rectified to linear scale from original optical recording Areas B E volume-elastic increments Areas A D F volume-elastic decrements C area of back flow Interrupted line MM mean flow level Line OO zero flow level Synchronous vertical intercepts for each curve reading consecutively are 1) Onset of flow and pressure rise 2) Maximal rates of forward flow and volume increase 3) Peak of applied pressure 4) Point of maximal intravascular volume 5) Maximal rates of back flow and volume decrease (Shipley Gregg and Schroeder [illegible])

responsible for the phasic alterations in rate of inflow (flow pattern)

Since an arterial vascular tree is functionally an expansible chamber as well as a tubular conducting system application of a central pressure head will give rise to a pulsatile change in the contained volume of that arterial tree The area enclosed by the mean flow line zero flow line and the two intercepts at beginning and end of a cycle in figure 37 represents the volume of blood passing through the bed Since the venous outflow can be represented as essentially a straight line area B and F above the mean flow line represent a volume of blood taken into the arterial tree in excess of that leaving the bed in the same time interval Similarly areas A C D I below the mean flow line represent an equal volume of blood which the vascular tree does not accept during the same cycle and which is less by the same amount as the volume of blood leaving the bed at the same time During the early systolic portion of the cycle the vascular tree has accommodated a volume greater than that which can run off peripherally during the late systolic and early diastolic portion and a back flow of blood is recorded In the femoral velocity curve in figure 37 the amount of excess which cannot at once be included in the peripheral run-off is indicated as a definite back flow (area below the zero flow line) Thus these pulsatile flow waves which accompany the pulsatile volume variations distal to the meter reflect the capacity of the arterial tree to distend and recoil during the cyclic rise and fall of the applied *pressure pulse*

In summary then since the rate of venous outflow from the femoral bed is essentially constant and since most of the distensible vessels lie outside the muscle mass fed by the femoral artery the mean flow line in figure 37 *presumably* represents the intramural rate of flow *Since in addition* the rate of venous outflow from the femoral bed is essentially the same as the mean rate of arterial inflow it follows that the algebraic difference between the arterial inflow and the rate of venous outflow *represents* the rate and direction of V E flow *i e* the flow pattern is a continuous graphic representation of the *rate* and direction of volume-elastic flow in the bed The volume-elastic flow although recorded as an axial flow is actually a radial displacement of blood within the vessels The direction of the radial displacement will depend upon the pressure gradient at the moment The pressure gradient is in turn determined by the character of the applied pressure pulse (central to the flow meter) and the volume-elastic properties of the arterial tree and adjacent extravascular tissues (peripheral to the meter) Whenever the rate of retrograde volume-elastic flow (centripetal intravascular recoil) exceeds the rate of peripheral outflow the arterial flow pattern will

reveal a back flow component Back flow will be recorded at the site of the meter whenever the applied perfusing pressure on the central side of the meter is less than the pressure produced peripheral to the meter as the result of the passive elastic recoil from the arterial tree and surrounding tissue (and the active extrinsically applied pressure in the case of the coronary arteries)

By graphic integration of the velocity curve, I, the corresponding volume pulse curve V has been constructed and placed in proper time relation with the velocity curve and pressure curve in figure 37 Phasic fluctuations in intravascular volume versus the accompanying fluctuations in applied pressure head constitute a special type of V-F relationship The dynamic factors of inertia and viscosity must introduce considerable variation in the magnitude and timing of the intravascular volume response to the applied pressure change As the result of inertia, the volume change may lag behind or possibly

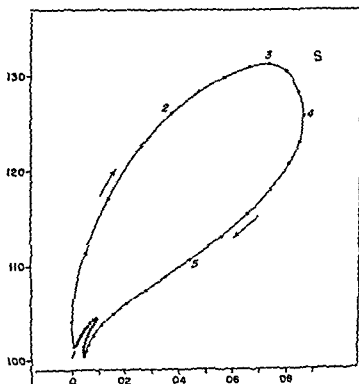


FIG 38 –Graph showing a continuous plot (dynamic V E curve) of applied pressure versus intravascular volume increment derived from flow curve, F figure 37 Ordinate applied intra arterial pressure in mm Hg Abscissa intravascular volume increment in cubic centimeters Dots on curve demarcate uniform time intervals (1/50 cycle length) Numbered dots indicate time relations of correspondingly numbered intercepts in figure 37 Arrows indicate direction of progression with time Interrupted line is presumptive trend of static V E curve (Shipley Gregg and Schroeder [4])

overshoot its corresponding change in applied pressure while viscosity would impose a considerable damping and retardation of the volume change. In this instance, it is obvious that the intravascular volume change lags behind the applied pressure change. The magnitude of the combined effects of viscosity and inertia can be better visualized when synchronous points on the two curves are plotted against each other (See Fig. 38). The dynamic volume-elastic relationship then appears as a continuous circuitous curve which is grossly different from the conceivable and probable simultaneously existing static volume-elastic curve (line S). As compared to the SVE curve the DVE curve is displaced first away from the volume axis during the major pressure rise and then toward the volume axis as the pressure falls. This lag of the volume change behind pressure change throughout the cardiac cycle presumably arises largely from the dynamic effects of viscosity.

Such considerations have been most helpful in understanding the mechanism of peripheral flow. Unfortunately, the analytical approach for peripheral patterns does not encompass all the factors which comprise the determinants of the coronary flow patterns. The coronary flow patterns are more complex and a similar analysis for them has not been found possible because coronary venous outflow is markedly pulsatile and the coronary arterial pattern is greatly influenced by compression and relaxation of extrinsic origin (extravascular support). However, much has been learned from a descriptive approach to the coronary flow patterns.

In figure 39 is a reproduction of a typical normal phasic flow curve obtained from the anterior descending branch of the left coronary artery with the orifice meter and which has been redrawn to a linear ordinate scale. Approximately at the onset of isometric contraction the rate of flow abruptly begins to diminish and soon passes below the zero line to appear as back flow. With the onset of ejection from the ventricle and the rise of aortic pressure, back flow diminishes and is rapidly converted to forward flow which reaches a maximum shortly before the peak of the aortic pressure curve. It then declines, leveling off during the latter part of systole. Coincident with the closure of the aortic valves and onset of isometric relaxation the inflow again rapidly augments and thereafter gradually declines with the diastolic fall of aortic blood pressure.

Information concerning phasic blood flow and its determinants in the right coronary artery is not abundant. Typical curves are reproduced in figure 36. Reconstruction to a linear ordinate scale (Fig. 39) shows that the points of inflection with reference to the phasic blood pressure are the same as those for the left coronary

artery The velocity curve tends to follow that of the central coronary pulse, while the velocity of *systolic flow may approach or exceed* the diastolic rate of flow At no point in systole does the rate of flow approach zero or become back flow as it so often does in the left coronary artery

Phasic flow in the left anterior auricular artery of the heart lung preparation shows a forward flow in the auricular artery in both systole and diastole, with the flow pattern resembling the aortic pressure curve [11] Since the published aortic pressure pattern is atypical, interpretation of these phasic curves is difficult

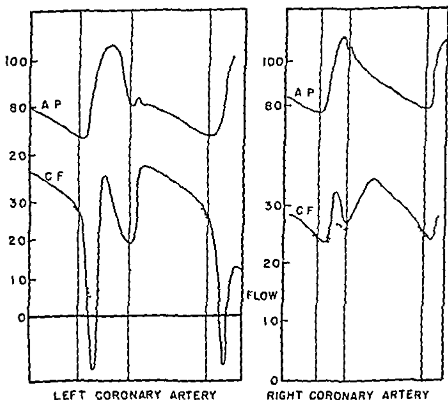


FIG 39 —Reconstruction and comparison of typical flow curves obtained with the orifice meter from the anterior descending branch of the left coronary artery in a small dog, and from the right coronary artery in a large *dog* AP, aortic pressure CF coronary inflow Ordinates upper mm Hg *lower*, flow in cc per min Vertical intercept demarcate systole and diastole Dotted lines predicted intramural velocity curve

Phasic variations in flow in the coronary veins during the cardiac cycle have *been recorded by Johnson and Wiggers* [14] with the Pitot tube in the anesthetized open chest dog A sizeable outflow of blood from the coronary sinus is present throughout most of the

cardiac cycle (Fig. 40). There is one large wave during systole. With the onset of the isometric contraction period, systolic flow rises abruptly to reach a peak at the beginning of protodiastole and then decreases gradually to reach its lowest velocity late in diastole. During diastole, the velocity of flow progressively decreases to approximate zero at its end.[3,30] The fact that during late diastole flow through the coronary sinus is negligible but is large into the coronary arteries and through the myocardium is taken to mean that most of the venous flow at this time operates to distend the coronary venous system.

Cyclic changes in blood flow through the anterior cardiac veins have never been measured due to technical difficulties. A general pattern and distribution of flow similar to that in the coronary sinus would be expected.

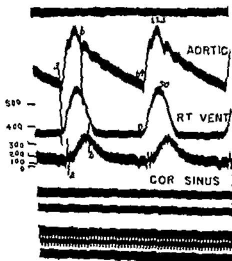


FIG. 40.—Reproduction of record showing velocity of blood flow in the coronary sinus of the dog as obtained with Pitot tube. Upper curve, aortic pressure; middle curve, right ventricular pressure; lowest curve, coronary sinus flow (flow beam read at bottom). Ordinate, coronary sinus flow, cc. per min. Time 0.02 sec. (Johnson and Wiggers.[30])

While such flow curves represent the normal flow at a coronary inlet or outlet, the use of the moment-to-moment rate of inflow and outflow to interpret the mechanism affecting flow requires detailed analysis. These flow records are complicated by volume-elastic effects due to the cyclic rise and fall of aortic or atrial pressure and by a compressor action on the coronary vessels by ventricular sys-

artery *The velocity curve tends to follow that of the central coronary pulse*, while the velocity of systolic flow may approach or exceed the diastolic rate of flow At no point in systole does the rate of flow approach zero or become back flow as it so often does in the left coronary artery

Phasic flow in the left anterior auricular artery of the heart lung preparation shows a forward flow in the auricular artery in both systole and diastole with the flow pattern resembling the aortic pressure curve[11] Since the published aortic pressure pattern is atypical interpretation of these phasic curves is difficult

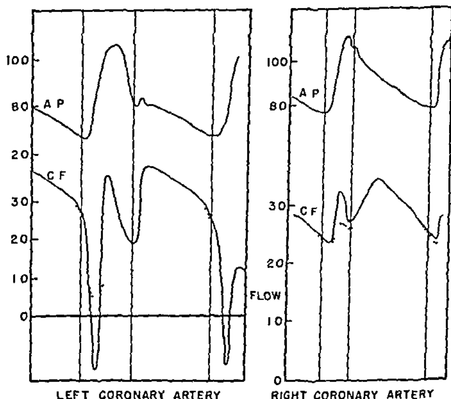


FIG 39 —Reconstruction and comparison of typical flow curves obtained with the orifice meter from the anterior descending branch of the left coronary artery in a small dog and from the right coronary artery in a large dog AP aortic pressure CF coronary inflow Ordinate upper mm Hg lower, flow in cc per min Vertical intercept demarcate systole and *diastole* *Dotted lines predicted intramural velocity curves*

Phasic variations in flow in the coronary veins during the cardiac cycle have been recorded by Johnson and Wiggers[30] with the Pitot tube in the anesthetized open chest dog A sizable outflow of blood from the coronary sinus is present throughout most of the

of systole at or just preceding protodiastole, and at the end of diastole just preceding isometric contraction are the factors relating to extramural flow at a minimum and hence the metered inflow may only then approximate a true measure of intramural flow. If at these two points the intramural factors were completely removed, separate estimates could be made of the two important factors controlling intramural flow, i.e., the state of contraction of the coronary vessels and their extravascular support. This would be possible because at the end of diastole extravascular compression is at a minimum while at the height of intraventricular pressure compression is at a maximum.

While the magnitude of the alterations of the intramural flow curve by these extramural factors has never been satisfactorily quantitated, possible patterns for intramural flow in the two coronary arteries which would follow from the preceding analysis are included in figure 39 as dotted lines.

The venous outflow curves can be similarly analyzed with the points of minimal extravascular effect being also at late diastole and late systole.

The effects on the flow pattern of changes in blood pressure, heart rate, resistance load, cardiac nerve stimulation, valvular deficiencies and drugs are multiple and have been separately reported[5, 8, 13, 15, 18, 19, 20, 23] and will be considered later.

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tole Hence, during a considerable portion of the cardiac cycle the rate of inflow at the coronary ostium or outflow into the right atrium and flow through the myocardium must differ The main factors controlling intramural flow are probably, (*1*) the aortic head of pressure, and (*2*) the resistance to flow which in turn is dependent upon the degree of contraction of the intrinsic muscles of the coronary vessels and the extent of extravascular compression or support The factors causing the total rate of inflow or outflow to be greater or less than intramural flow are, (*1*) the compressor action of ventricular systole on the coronary vessels and (*2*) the volume-elastic effects produced by the pulsating aortic or atrial pressure With *these factors in mind, it is desirable to know to what extent such* curves represent events in the coronary bed within the myocardial walls

A possible picture for the latter referred to the coronary inflow curve is as follows During isometric contraction and early ejection the blood in the deeper lying and more strongly compressed coronary vessels is forced backward into the larger proximal channels and by *thus contributing to the supply of blood available for the less strong*ly compressed and more superficial vessels reduces the inflow from the aorta This fact is demonstrated by the rise of peripheral coronary pressure and by the back flow recorded by the constant pressure flow meter at appropriate low perfusion pressures during isometric contraction and early ejection As the aortic pressure continues to rise the extramural flow increases due to the increased distention and therefore greater capacity of the more superficial vessels This effect also ceases at the peak of aortic pressure or slightly later due to the inertia of the moving column of blood During isometric relaxation and early diastole the compressed myocardial vessels are rapidly released thus causing the total inflow to exceed the actual intramural flow As aortic pressure drops the expansion of the superficial coronary vessels is *slowly reduced thus decreasing the total rate of inflow below the intramural flow* At the *end of diastole* both effects are minimal

The magnitude of these effects is enough to produce considerable alterations of the inflow curve Constant flow meter studies[14] have shown that ventricular contraction and relaxation may reduce left coronary inflow during systole by 50 per cent and augment early diastolic flow by 20 to 50 per cent Volume-elastic studies on the coronary vessels[6] *indicate similarly that the change in capacity of* the vessels as a result of the cyclic change of aortic pressure may reach 25 to 50 per cent of the systolic flow

From such an analysis it is deduced that only during the last part

30 JOHNSON J R and C J WIGGERS The alleged validity of coronary sinus outflow as a criterion of coronary reaction Am J Physiol 118 38 1937
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Chapter 6

THE DETERMINANTS OF CORONARY BLOOD FLOW AND THEIR EVALUATION

ACCURATE estimates of the changes in the gross vasomotor state of the coronary vascular bed are of first importance to an understanding of the mechanisms which control coronary flow. The determinants of coronary flow have been partially indicated in consideration of the phasic flow curves. As in any other vascular bed the influences controlling coronary blood flow are comprised of both physical and chemical factors. The flow varies directly with the size of the vascular bed, the pressure head and inversely with the back pressure at the end of the system and the viscous resistance encountered in transit through the entire bed. Aortic blood pressure determines the head pressure applied at the coronary orifices; right atrial pressure (and to a smaller extent, pressure in the right ventricle) determines venous back pressure. Viscous resistance to flow is determined by the static and dynamic effects of the viscosity of the blood and the bore of the blood vessels. In the smallest caliber arteries the mean pressure approximates that at the aortic valves while in the capillaries the pressure approximates 15 to 25 mm Hg. Hence most of the vascular resistance to flow or change in vessel caliber affecting peripheral resistance lies in the arterioles or vessels of the order of 1 millimeter in diameter. Their bore may be altered by 3 factors: passive compression and relaxation resulting from rhythmical myocardial contraction (extravascular support); active vasomotor changes in the vessels induced by nervous and/or humoral influences upon their intrinsic muscles and the internal applied pressure head.

METHODS FOR ESTIMATING DETERMINANTS OF BLOOD FLOW CHANGES

Changes in aortic or central coronary pressure, venous, atrial and ventricular pressure can be readily determined by the use of appropriate procedures and pressure manometers[43, 53] as indicated in Chapter 3.

Viscous resistance to coronary flow is governed for the most part by the mean caliber of the coronary vascular bed. Since by definition total peripheral resistance (TPR) in the coronary vascular bed

equals mean central coronary pressure/mean coronary inflow changes in the gross vasomotor state (TPR) of the coronary bed can be recognized by correlating as a simple ratio the central coronary pressure with the corresponding mean coronary inflow Thus a change in either the flow or pressure without change in the other would indicate a change in TPR (mean bore of the coronary bed) while a proportionate change in both flow and pressure would indicate no alteration in TPR However the application of such an index is limited and must be made with caution Such an index does not take into account viscosity effects which in a dynamic system may give rise to considerable variation in the relationship of mean pressure to mean rate of flow for which appropriate in vivo correction curves are not available[81] Nevertheless a gross change in the vasomotor state of the coronary bed can be regarded as having occurred when a large increase in coronary inflow is induced without change in central coronary pressure when coronary inflow decreases greatly without an increase in coronary pressure or when flow and pressure undergo large changes in opposite directions

Only partial success has resulted from attempts to identify and estimate separately the changes in the two important (per se) variables which control the caliber of the coronary vessels namely active vasomotor changes in the vessels induced by nervous and/or chemical influence upon their intrinsic muscles and extravascular compression (support) and relaxation

As yet unsolved is the problem of determining the relationship of blood flow *to active* vasomotor changes irrespective of whether the effect on the intrinsic muscles of *the coronary* vessels is mediated through the blood *stream* or is secondary to metabolic changes in the surrounding myocardium It is not known how much coronary flow might change with a *given* change in coronary perfusing pressure without an associated active *change* in the vasomotor state of the bed Determination of active variations in vasomotor tone in the coronary bed is further *complicated* by uncontrollable mechanical factors Variations may occur in the respective durations of systole and diastole in which periods the rates of flow per unit of time may be quite different and thus obscure any *active* vasomotor changes

It has been suggested that by analysis of phasic inflow curves such as those described *earlier* (*Chapter 5*) that changes in the vasomotor state and extravascular support can be separately determined Critical points on flow curves have been selected in late diastole and systole at which time the *rate* of change of the volume-elastic and myocardial compression forces are presumed to be minimal[65] At the *diastolic* point extravascular forces are at a minimum and the

rate of flow reflects the vasomotor state of the coronary bed at the systolic point, extravascular support is maximal and the flow is said *to reflect the combined effect of myocardial compression and the* existing vasomotor state At these points the ratio of the aortic pressure to the simultaneously existing rate of flow is determined (*See* Fig 39 p 98) A shift in the diastolic ratio is taken to represent active constriction or dilatation of the coronary bed Changes in the extravascular compressing force are determined by comparing the systolic and diastolic ratios [1, 37] Such deductions require the necessary proof of the ability of an indirect analysis to indicate correctly the actual occurrences Some of the assumptions upon which the validity of the method must necessarily depend are, that (*1*) a time period exists in which, throughout most of the myocardium contraction of the myocardial fibers on the lumina of the whole coronary bed is exerted essentially simultaneously (2) rates of flow taken at the critical points represent flow through the myocardium, (3) rate of flow is linear in both systole and diastole with respect to pressure Until these are verified experimentally such a system of interpretation cannot be regarded as having a sound hydrodynamic basis

The problem of determining the magnitude of extravascular support has been approached in different ways It has been suggested that intramural pressure can be used as a measure of extravascular compression and attempts have been made to quantitate the pressure developed within the wall of the left ventricle during systole and to use it as a measure of extravascular support Johnson and Di Palma[60, 61] inserted an artery segment through the left myocardial wall parallel to the left descendens and at different depths One end of the segment was connected to an optical manometer and the other end to the pressure system supplying the manometer The artery segment was initially inflated to 200 mm Hg or more, to give a rigid system so that any pressure increment applied to the outside surface of the artery would produce a constant and equal increment of pressure on the inside By this means it was believed possible to determine the pressure developed by the myocardium as it contracted against the embedded artery segment by measuring the rise in pressure within the artery during systole It was found that when the artery was placed superficially in the left myocardium the recorded intramyocardial pressure pulse varied from less than to greater than the aortic systolic pressure when the segment was placed at a depth about one half the ventricular wall thickness the pressure pulse recorded always considerably exceeded the aortic systolic pressure In similar experiments Gregg *et al* [44] also found that the pres

ure pulse recorded from an imbedded vessel (or myocardial pocket of fluid connected by needle to an optical manometer) generally was considerably greater than the aortic pressure (Fig. 41 A B). However on the basis of further experimental work these pressures are believed to be in part artefactually produced and hence not to approximate the correct value for intramural pressure or to demonstrate crucially that intramyocardial pressure exceeds ventricular pressure during systole. In support of this disbelief are the following experimental findings. (1) The pressure pulse from an intramyocardial pocket of fluid increases progressively to values greater than aortic systolic pressure upon raising the diastolic pressure in the

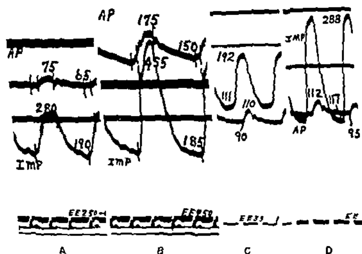


FIG 41 —A B reproduction of segments of records showing the comparative effect of aortic constriction on the pressure pulses recorded from the aorta and from an arterial segment imbedded in the left ventricular wall. C aortic pressure and pressure pulse from a vessel segment protected by a fenestrated metal sleeve and imbedded parallel to the left descendens and to approximately one-half the depth of the myocardium. D after removal of protective sleeve. AP aortic pressure IMP intramural pressure. Time 0 2 sec (Gregg and Eckstein [4])

pocket of fluid and hence it could well be a function of the degree of localized muscle stretch induced by the applied internal pressure. (2) When blood from the aorta flows through a deeply imbedded segment a systolic flow often occurs. (3) Pressure pulses recorded from a vessel segment in the left ventricular cavity (or wall) may have 2 to 4 times the ordinate value of the intraventricular pressure although usually the values are somewhat lower. (4) Protection of the segment in the cavity or wall by a loose fitting fenestrated cup

or retractible fenestrated sleeve reduces the recorded pressure pulse in the left ventricular cavity to values approximating aortic systolic and in the myocardium, to values approximating or somewhat less than aortic pressure (Fig 41 *C, D*) However theoretical and experimental evidence (from a mechanical model) showed that pressure transfer exceeds considerably 100 per cent when there is movement and distortion of the segment and that transfer through a protected segment is generally not complete From this, it is felt that although the use of vessel segments may give directional changes, accurate quantitative measurement is not possible by this method

The maximum pressure transmitted during systole from the myocardium into a coronary artery peripheral to the point of temporary occlusion of that artery, has been recorded in many dynamic states and has been used as an index of extravascular compression,[4] (*See* Fig 17 p 52) However in such a system, elevation of the intracoronary vessel pressure during systole is related not only to the external compressing force of the myocardial fibers but to the relative fulness of the bed and the ease with which the trapped blood can run off peripherally through the capillaries (vasomotor state) In order that changes in extravascular compression may be accurately indicated it is necessary that the vasomotor state of the bed and its relative fulness remain unchanged Since it is not possible to control or predict the constancy of these variables, the method should not be used

EVALUATION OF CORONARY FLOW DETERMINANTS UNDER DIFFERENT DYNAMIC CONDITIONS

The blood supply of the heart must be rapidly adapted to its suddenly changing needs How this adaptation is effected is of the utmost importance The pressure relations in the coronary arteries and coronary veins the cardiac nerves and possible reflexes changing input and output loads the blood chemicals gases and heart rate must all be considered Different views have been expressed as to the dominant controlling mechanism

1 Coronary flow may be largely governed passively by the aortic (or central coronary) pressure the degree of extravascular support and the pressure in the right atrium Thus changing cardiac output peripheral resistance, and heart rate would largely alter coronary inflow by variations in central coronary pressure extravascular support, and right atrial pressure

2 Coronary flow may be altered by reflex action of the cardiac

nerves directly on the intrinsic smooth muscles of the coronary vessels causing them to relax or to constrict

3 Coronary flow may be automatically adjusted to the metabolic needs of the heart by active coronary dilation or constriction induced by local chemicometabolic influences arising from changes in the metabolism (and work) of the heart

4 The coronary flow change may arise from combinations of these possibilities weighted differently

In past studies of the determinants of coronary blood flow the venous drainage systems of the two ventricles were considered to operate in fundamentally different ways and local mechanical forces were believed to be more potent in regulating flow than the chemical or humoral influences There has been a tendency to stress results obtained in situations where although certain flow determinants were easily and completely controlled it was neither possible to gauge the physiological normalcy of the preparation nor to determine the influence of the uncontrollable variables Recent studies in the dog have led to a re-examination of certain beliefs inasmuch as several new anatomical and functional concepts have arisen concerning the coronary venous system collateral the coronary flow response to drugs to increased cardiac load and to cardiac nerve stimulation Such modifications of our working knowledge of the coronary circulation has followed the introduction of new methods and instruments and new and revised experimental procedures

Coronary Arterial Blood Pressure —The mechanisms concerned in alterations of coronary flow following acute elevation or depression of central coronary pressure have been only partially elucidated It is easy to demonstrate in the dog with the heart beating *in situ* that coronary inflow increases greatly when a coronary artery (right or left) is perfused with blood from a constant pressure flow meter at progressively increasing pressures or that the inflow decreases as the perfusion pressure is lowered Following an acute increase in aortic blood pressure by a clamp on the aorta flow measurements in the left coronary artery with the orifice plate meter [20] rotameter [17] constant pressure meter [4] and bubble flow meter [22] with the dog s heart beating *in situ* all indicate that the mean flow increases considerably As recorded with the orifice meter both the systolic and diastolic flows increase throughout the cardiac cycle (Fig 42) With increased aortic pressure right coronary inflow also increases [5] Similarly as aortic pressure decreases rather gradually either spontaneously or with histamine or procaine injection (subdural) left coronary inflow also generally decreases [22]

However in both right and left hearts there is no set relationship

between coronary flow and the aortic or central coronary pressure change the effect on flow of a given pressure change varying from zero to a very large one Right or left coronary inflow (as measured by an orifice meter or rotameter with the infusion pressure kept

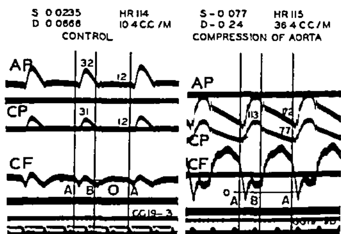


Fig 42 —Reproduction of records showing the effect of aortic compression on blood flow in the left descendens artery Vertical lines A, B approximate ends of diastole and systole AP aortic pressure CP, central coronary pressure CF coronary inflow Ordinate, rate of flow in cc /min S and D flow during systole and diastole O zero flow Time 0 2 sec (Green and Gregg [35])

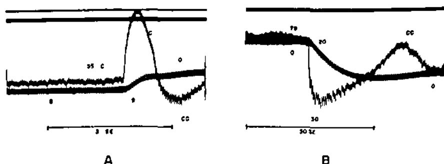


Fig 43 —Reproduction of records showing the effect of aortic constriction (A) and release (B) on total left coronary inflow as measured with the rotameter Detail in text

constant) may increase greatly when right or left ventricular pressure is elevated by a pulmonary artery or aortic clamp [49, 51] Such a trend for the right coronary artery is illustrated in experiments 12 15 of Table 2 p 81 This lack of correlation of pressure and flow is especially evident when aortic pressure is abruptly increased or decreased by an aortic clamp The flow changes in the left coronary

artery with both procedures are illustrated in figure 43 In figure 43 A the coronary inflow initially rises and then falls considerably while central coronary pressure is progressively rising following mechanical constriction of the aorta In this instance calculations indicate that the total peripheral resistance (pressure/flow) decreases greatly from 1 45 to 0 76 during the peak of the flow curve and then increases greatly to 2 75 as the flow falls In figure 43 B the reverse flow changes occur i e as aortic blood pressure progressively falls following abrupt release of the aortic clamp the coronary flow initially decreases and then increases During this time the calculated total peripheral resistance increases during the trough of the flow curve from 1 9 to 4 0 and then decreases greatly to 1 1 as the flow

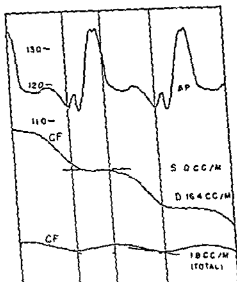


FIG 44 Tracing of original curves to show the peripheral resistance to flow in the anterior descending branch of the left coronary artery Upper curve (AP) aortic pressure Middle curve flow curve with coronary artery perfused at a constant pressure of 82 mm Hg Lowest curve flow curve with coronary artery perfused at 12 mm Hg Figures at right indicate the rate of flow at mid systole and late diastole for the two flow curves Vertical line A B indicate systole and diastole

rises Although these changes must arise either from active or passive alteration in the mean bore of the coronary bed at present an adequate explanation of such flow changes is not available due to lack of adequate methods for investigation The fact that the decrease in TPR with increased blood pressure in figure 43 A and the increase in TPR with decreased blood pressure in figure 43 B are

well under way before a significant change in blood pressure suggests that the alterations in peripheral resistance are in part under nervous influence The delayed increase in TPR in figure 43 A could well arise from the earlier over oxygenation or washing out of local metabolites from the myocardium The delayed decrease in peripheral resistance in figure 43 *B* could well be related to the probable anoxia or the accumulation of metabolites during the preceding period of reduced coronary flow Finally the calculated changes in periph

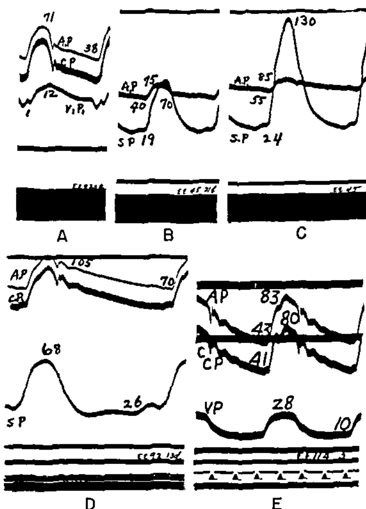


Fig 45 —Reproduction of records showing comparison of pressure curves from the aorta (AP) coronary artery (CP) and the coronary sinus or great cardiac vein (SP or VP) under different dynamic conditions and with different degrees of venous constriction A normal relationship B and C coronary sinus pressure immediately following sinus occlusion D coronary sinus closed and pressure measured through a branch of the great cardiac vein E great cardiac vein pressure one month after coronary sinus ligation Time 0 02 and 0 2 sec

eral resistance are in part related to the experimental fact observed some years ago that as in the renal[18] and other vascular beds an infinite resistance to coronary flow exists in the presence of a sizeable coronary pressure i e coronary inflow ceases when coronary perfusion pressure is still considerable This is illustrated in the flow curves reproduced in figure 44 which are typical of many such experiments In this the anterior descending branch of the left coronary artery was perfused at a constant pressure by the method of Gregg and Green[56] As the coronary perfusion pressure was progressively lowered forward flow during the cardiac cycle essentially ceased at a perfusion pressure of 12 mm Hg

Coronary Venous Pressure – The venous pressure in the great cardiac vein of the anesthetized dog with or without open chest approximates $\frac{10\text{-}15}{0\text{-}5}$ mm Hg (See Fig 46 A)[22,56] the values for the coronary sinus and anterior cardiac veins are considerably lower while that in the right atrium into which the coronary blood drains approximates 0-8 mm Hg Their effect on coronary inflow is not known If the systemic venous pressure or right atrial pressure is increased one would expect that the pressure increase would be transmitted to the coronary veins which empty into the right atrium and that the resultant increase in coronary venous pressure would decrease both right and left coronary inflow However the influence of these pressures on coronary flow is difficult to study for the induced changes in them lead to other cardiodynamic alterations An approach to the problem has been made by studying the effect of ligation of the coronary venous drainage system on coronary inflow With the heart beating *in situ* acute coronary sinus closure causes congestion of the left ventricle (but not of the right ventricle or atria) a greatly elevated *venous pressure in the coronary* sinus and great cardiac vein often approximating or exceeding aortic systolic pressure[47,56] (Fig 45 *I C D*) but the flow reduction in the left coronary artery or its major branches is small averaging 8 per cent in 10 dogs[50] (Table 5 expts 5 and 6) However the venous outflow measured simultaneously in several major anterior cardiac veins increases greatly (Table 5 expts 5 and 6) Similar responses occur when the major venous drainage channels of the right heart the anterior cardiac veins are occluded in acute experiments right coronary inflow decreases from 0 to 63 per cent averaging 21 per cent in 8 different experiments (Table 5 expts 7 and 8)

In acute experiments pulmonary artery constriction in the presence of previous ligation of the anterior cardiac veins still causes a significant augmentation of right coronary inflow (Table 5 expt 3)

Table 5.—Effect of Superficial Coronary Venous Stasis on Coronary Blood Flow

Expt No	*Mean Aortic Pressure* Before mm Hg	*Mean Aortic Pressure* During mm Hg	*Arterial Inflow* Before cc/min	*Arterial Inflow* During cc/min	*Venous Outflow* Before cc/min	*Venous Outflow* During cc/min	*Remarks*
			Right Coronary		AC veins		
1	95	92			4.2	13.2	Coronary sinus occlusion (4 min) on AC vein flow. Flow measured in AC vein nearest pulmonary conus
2	90	90			5.0	12.6	Coronary sinus occlusion ([illegible] min) on AC vein flow. Flow measured in 3 of 4 major AC veins
3	67	67	16	19			Pulmonary artery constriction vs right cor flow with all major AC veins previously ligated. Right ventricular pressure rose from 15.0 to 30.2 mm Hg
4	7[illegible]	72	9	12.5			Pulmonary artery constriction vs right coronary flow with all grossly visible AC veins and coronary sinus ligated 5 min previously. Right ventricular pressure rose from 13.0 to 4[illegible].2 mm Hg
			Left Circ				
5	103	10[illegible]	20	21			Coronary sinus occlusion (6 min) vs left circumflex flow (minimal effect)
6	80	80	20	10			Coronary sinus occlusion (3 min) vs left circumflex flow (maximal effect)
			Right Coronary				
7	92	90	14	6			Occlusion of major AC veins vs right coronary flow (maximal effect)
8	100	95	11.5	11.[illegible]			Occlusion of major AC veins vs right coronary flow (minimal effect)

Finally, occlusion of both the coronary sinus and all grossly visible anterior cardiac veins reduces inflow further but the hearts generally survive and coronary inflow increases with increased load (Table 5, expt 4). Even with chronic ligation of the anterior cardiac veins and the coronary sinus, the peripheral coronary venous pressure returns toward normal within 30 days[85] (Fig 45 *I*).

From these observations it does not seem likely that a considerable elevation of right atrial pressure will influence significantly coronary inflow in the normal heart.

Extravascular Support.—As indicated earlier, there are no experiments or methods by which changes in this important determinant of coronary flow can be unequivocally detected in the beating heart.

Presumably extravascular support is abruptly and largely reduced when ventricular fibrillation occurs for coronary inflow increases immediately and greatly when the coronary vessels are perfused at a constant pressure [3,55] However it must be borne in mind that concomitantly cardiac carbohydrate metabolism increases [55] which is also known to be associated with an increase in the mean bore of the coronary bed

Effects of Asphyxia Anoxia Hypercapnia, and Myocardial Ischemia on Coronary Inflow – The chemical composition of the blood and tissue fluids within the heart has been found to be of great importance in determining the volume of coronary flow

Asphyxia in which the carbon dioxide content of the blood increases and the oxygen content decreases simultaneously from cessation of breathing is accompanied by a large increase in coronary inflow in the anesthetized dog Within thirty to sixty seconds after cessation of respiration the flow in both systole and diastole increases averaging about 200 per cent and occurs before any significant change in aortic pressure or heart rate [38]

When the oxygen content of the arterial blood is decreased by breathing mixtures of air and nitrogen or oxygen utilization is prevented by the injection of cyanide the resultant anoxia induces profound increases (200 to 300 per cent) in coronary arterial inflow in the anesthetized dog [4,38] heart lung preparation [55] isolated heart [9] and fibrillating heart [64] The increase in coronary inflow precedes any change in heart rate or blood pressure and maximal dilatation occurs when the arterial saturation falls to 20 per cent (heart lung preparation) and to 50 per cent (heart *in situ*) of normal oxygen capacity

Carbon dioxide added to the air inhaled in concentrations of 5 to 8 per cent can be administered until slowing of the heart premature systoles and decline of aortic pressure occur but without significant change in mean or phasic coronary inflow [24,38] However in the heart lung preparation [63] and isolated perfused revived human heart [6] administration of carbon dioxide leads to a considerable increase in coronary inflow

After release of temporary occlusion of a coronary artery mean coronary inflow increases almost immediately in the isolated heart [20] heart lung preparation [54] and in the dog s heart beating *in situ* [4,24,38,4] The augmented flow exists throughout systole and diastole (Fig 46) is maximal (200 to 300 per cent of the control) within about forty five seconds and returns to normal within one to three minutes The maximal flow response occurs without blood pressure or heart rate change and is generally reached before a significant impairment

of myocardial contraction occurs (as indicated by a lack of systolic extension recorded with the myograph) When a coronary artery is only moderately constricted, the flow is only temporarily reduced and may return to the control level unless the degree of constriction is extreme Presumably, this compensatory vasodilation exists in man and operates to avoid the untoward effects of temporary ischemia which may appear during exercise and angina pectoris

Resistance changes can be demonstrated in the coronary bed when the vessels are perfused at various pressures with the cardiac work kept constant [1] When, in the open-chest dog the left coronary

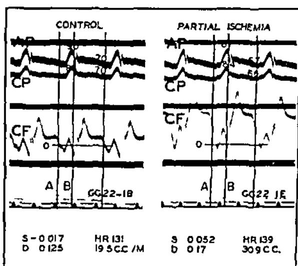


FIG 46—Reproduction of records showing the effect of temporary ischemia on blood flow in the ramus descendens anterior CP coronary pressure CF, coronary inflow AP aortic pressure vertical lines A B indicate approximate end of diastole and systole S and D flow during systole and diastole Time 0 2 sec (Green and Gregg [35])

artery is perfused at a constant pressure and inflow is measured by a rotameter or orifice meter there is a rapid and marked increase in coronary vascular resistance within a few seconds following elevation of the perfusion pressure from aortic to a pressure above aortic Similarly when the perfusion pressure is decreased below aortic there is a marked reduction in vascular resistance It is believed that these changes represent automatic shifts in the size of the coronary vascular bed and in vascular resistance which serve to meet the metabolic needs of the myocardium Whether they are related to the oxygen supply and demand or to the relative amount of metabolites washed away is not known

In summary since the coronary flow response to hypercapnia is

negligible whereas the flow effect of systemic anoxia produced by artificial respiration with air and nitrogen and of local anoxia by under perfusion and myocardial anoxia produced by cyanide injection into the coronary artery are similar it is concluded that they all depend upon the anoxia produced and probably upon this anoxia being present in the myocardium Since the blood pressure does not change and the ratio of pressure to flow increases throughout the cardiac cycle it is also concluded that anoxia causes a relaxation of the walls of the coronary vessels To what extent this is active that is a direct effect on smooth muscle of the coronary vessels and to what extent if any extravascular support has been lowered cannot be told in these experiments although efforts have been made to do so [38]

The mechanism by which anoxia operates to increase coronary inflow is not clear Presumably in this situation metabolites accumulate but their nature is unknown In the heart lung preparation coronary inflow generally progressively increases as the experiment continues and substances accumulating in the venous blood apparently cause coronary dilation when reinfused into the coronary arteries [71, 74, 5] However Hilton and Eichholtz[55] could not confirm this for replacement of the blood that had circulated for some time by fresh defibrinated blood did not significantly alter the coronary flow Similarly coronary flow is increased when with the heart beating *in situ* coronary sinus blood or mixed venous blood is infused into the coronary arteries [24] Histamine and metabolites such as adenosine adenine adenylic acid and break-down products of nucleic acids increase the coronary flow in the human heart lung preparation and heart *in situ* [1, 35, 88] However it remains to be demonstrated that the concentrations of these substances increase within the myocardium during anoxia or increased effort of the heart

Responses of Coronary Circulation to Augmented Load —Of particular interest has been the subject of the coronary flow response to changes in the working load of the right and left hearts In experiments with the heart lung and comparable preparations (but excluding those in which the vagi are intact) elevation of right ventricular pressure by constriction of the pulmonary artery or elevation of left ventricular pressure by aortic constriction (coronary perfusing pressure kept constant) has been demonstrated to cause a reduction in blood flow to the myocardium of the right and left hearts respectively [12, 65, 66] The flow decrease is attributed to the dominant effect of the direct mechanical inhibitive action of the increased vigor of the heart and/or the establishment of an unfavorable pressure gradient especially for the right coronary artery drainage via

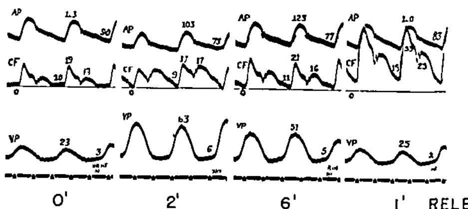


Fig 47 —Reproduction of a series of records showing effect of progressive increase in right ventricular pressure upon phasic right coronary inflow as measured with the orifice meter. AP, aortic pressure; CF, right coronary inflow; VP, right ventricular pressure. Time, 0.2 sec.

Fig 48 —Reproduction of four sections of records showing effects of progressive increase in right ventricular pressure upon coronary sinus flow. In each section: Upper, aortic pressure; middle, right ventricular pressure; lowest, coronary sinus flow. Vertical lines a, b, end of diastole and systole. Ordinate, coronary sinus flow, cc/min. Calibration refers to bottom of flow line. Time, 0.02 sec. (Johnson and Wiggers[6])

the Thebesian channels into the right ventricle. Such a response would seem to be one of poor economy and certainly would not be advantageous to the heart under an increased load. However, in more recent studies with the heart beating *in situ* and under somewhat more nearly normal physiological conditions with vagi and sympathetics intact or severed, directly measured right or left coronary inflow increased appreciably upon elevation of right ventricular pressure by pulmonary artery constriction or of left ventricular pressure by an aortic constriction central to the left coronary ostium.[49, 51] In addition, cardiac venous outflow in the coronary sinus[6] and the anterior cardiac veins increased greatly.[2] Reproductions of original curves showing that the flow into the right coronary artery and out of the coronary sinus increases in both systole and diastole are illustrated in figures 47, 48. Figure 49 A, B illustrates comparable changes in flow in the left coronary artery induced by this procedure.

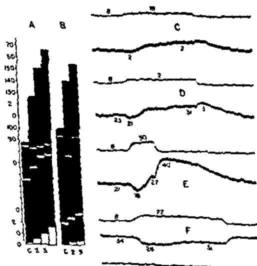


FIG. 49. Parts A and B. Bar graphs showing the effect of augmentation of left ventricular pressure on coronary inflow. Part A, left coronary inflow; part B, left circumflex inflow. Solid black bar, systolic and diastolic left ventricular pressures; hatched segment within each bar, aortic (coronary perfusing) pressure; white segment *within each bar*, coronary inflow. Abscissa: C, control; numbers denote minutes duration of aortic constriction. Common ordinate scale for all pressures in millimeters of mercury and flow in cubic centimeters per minute. Parts C, D, E and F, photographs of original records showing the effect of elevation of right ventricular pressure on right coronary inflow. Upper curve in each segment, mean right ventricular pressure with values in millimeters of mercury indicated by numbers adjacent to curve. Lower curve, mean right coronary inflow with values in cubic centimeters per minute indicated by numbers adjacent to curve. Time 5 sec. (Gregg *et al.*[51])

Although intra- and extracardiac reflexes cannot be positively ruled out as contributing factors in augmenting coronary inflow the facts that section of the vagi and of cardiac nerves from the sympathetic chain and application of procaine to the pulmonary conus and pulmonary artery all fail to abolish the coronary flow response mitigate against this view [49]

Associated with the elevated coronary inflow with augmentation of the load of the right or left ventricle the work and metabolism are also greatly increased the former arising from a decrease in cardiac output and an increased mean blood pressure the latter arising from a combination of an increased coronary flow and a greater extraction of oxygen from the coronary blood [49] These changes are illustrated for the right heart in Table 6 experiments 1, 2, and 3 The mechanism responsible for dilation of the coronary vessels under this condition cannot be identified with certainty However since the flow response rather closely parallels the change in work it is not improbable that the associated changes in metabolism are capable of effecting vasomotor regulation of the blood supply to the involved ventricle Two possible mechanisms can be advanced The coronary dilation results from (*1*) an increased local production and release of metabolites and/or (*2*) the creation of a local relative anoxia caused by a disproportion between the increased rate of oxygen utilization and the coronary blood flow partial (but not complete) compensation is accomplished by vasodilation and increased blood flow

That the local change in the heart may be small and yet effective in augmenting flow is indicated by experiments in which the effect of increased load on coronary inflow was tested while the control coronary inflow was artificially and greatly elevated by infusing blood into a coronary artery at a constant infusion pressure considerably above the prevailing central coronary pressure (Table 6 expts 5 and 6) Despite the presence of this plethora of flow (and with a considerably smaller oxygen arteriovenous difference) the coronary inflow (and coronary oxygen arteriovenous difference) were still further increased with augmented ventricular load [49]

Thus the two ventricles have at their disposal an internal compensatory means by which their blood supply can at least in part be adjusted to their work and metabolic requirements This sustained flow increase is taken to indicate a dominant influence of coronary dilation over the mechanical flow inhibiting effect of increased extravascular support As already indicated these results are diametrically opposed to those of other investigators using less normal physiological preparations

Regardless of the mechanism by which coronary inflow is increas

Exp	(1) Mean [illegible]	(2) Right Ventricular Systolic [illegible]	(3) Right Coronary Flow	(4) [illegible]	(5) Work [illegible] (3) (4)	A V O Diff	Comment	[illegible]
	[illegible]	18	10 0	680	[illegible] 00		Control	[illegible] work [illegible] right [illegible]
		43	13	698	000		Pulmonary artery constricted [illegible]	
1	[illegible]	45	13	[illegible]5	9 00		Pulmonary artery constricted [illegible]	
	80	[illegible]	15	5 0	33000		Pulmonary artery constricted 3	
	9[illegible]	[illegible]	15 8	[illegible]	38000		Pulmonary artery constricted 4 5 [illegible]	
				Oxygen [illegible]				
				Right Coronary [illegible] Vol %	Art Cardiac Vein Vol %	A V O Diff		
	9[illegible] 100	14	7 5	15 84	4 69	10 9	Control	Pulmonary artery constriction [illegible] difference and O2 utilization
	95 100	44	13 0	15 80	[illegible]	13 57	Pulmonary artery constriction	
	95 100	33	6 0	10 03	5 38	10 65	Recovery after release of pulmonary artery	
3	83	40	16 0	14 50	4 60	9 84	Control	
	80	64	20 0	13 [illegible]	3 12	10 63	Pulmonary artery constriction	
4	74	18	8 5	17 [illegible]5	7 80	9 80	Control	Illustrates [illegible] oxygen [illegible] arterial O2 capacity
	[illegible]4	40	10 5	10 25	0 3[illegible]	9 04	Pulmonary artery constriction	
	[illegible]	18	8 5	16 [illegible]5	[illegible]	9 08	Recovery	
5	80	1[illegible]	11 0	14 48	6 91	[illegible]	Control	Right coronary artery perfused at aortic pressure
	80	45	15 0	14 44	6 18	8 [illegible]	Pulmonary artery constriction	
[illegible]	80	17	11 0	13 51	10 43	3 08	Control	Right coronary artery perfused at 200 mm Hg pressure
	80	45	15 0	14 53	9 38	5 15		

ed, elevation of right or left ventricular pressure can also be shown to have a flow-reducing effect which operates in antagonism to the flow-promoting mechanism.[49] If, in the presence of an adequately maintained central coronary pressure, the pulmonary artery constriction and release are abrupt, the sustained flow increase described above may be preceded and followed by a transient period of flow reduction and elevation respectively, whose beginnings are coincident with the time of sudden constriction and release of the pulmonary artery (Fig. 49 *C* through *F*). The abrupt changes in coronary flow coincident with the onset of elevation and reduction in ventricular pressure are regarded as indications of a temporary separation of the influence of change in extravascular compression upon coronary flow. This conclusion is made with reasonable justification, since the increase or decrease in mechanical compression of the coronary vessels should occur simultaneously with the increase or decrease in intraventricular tension while the slower physiological metabolic and vasomotor responses must necessarily lag somewhat behind their respective exciting causes, *i. e.* the sudden changes in cardiac work. The initial temporary decrease in flow can be attributed *to the dominant influence of augmented extravascular mechan*ical compression of the coronary vessels. The subsequent appearance of an increased flow observed shortly thereafter indicates that the effect of coronary dilation has exceeded the flow-reducing effect of the increased extravascular compression. The immediate and *transient flow increase following abrupt lowering of intraventricular* pressure is a rough index of the extent to which flow had previously been retarded by the augmentation of extravascular compression.

These changes in coronary inflow demonstrate what is believed to be the "normal" relationship between increased ventricular load *and coronary flow. Under these conditions*, the net physiological response is directed toward augmenting the coronary blood supply in spite of the flow limiting effect of increased extravascular compression. However, if such experiments are intentionally prolonged (four to five hours) the coronary flow response to pulmonary artery *constriction is now reversed and the effect of a sustained and unalter*ably dominant influence of extravascular compression can be demonstrated. In figure 49 *F* the right coronary flow response is now a sustained decrease followed by a return to the control level upon release of the pulmonary artery. Thus in the latter stages of an *experiment during which the condition of the heart in situ* has progressively become far removed from normal the flow reducing effect of increased extravascular support is dominant over whatever flow promoting mechanism the heart has retained and would appear

to be left almost unopposed by any concomitant dilation of the coronary bed

In any event the inability of the heart to increase or even maintain its blood supply in the presence of an augmented load indicates an almost complete lack of reserve The heart must be regarded as having suffered some change or loss of its physiological mechanisms which event makes impossible the observations of these occurrences previously existent under more nearly normal physiological conditions As measured under these conditions and by others using heart lung preparations a decrease in coronary flow cannot be regarded as the normal response to an increased cardiac load

In the foregoing it was indicated that the trend of the coronary flow response to an augmented resistance load is the same for right and left ventricles In all types of heart preparations central coronary artery pressure elevation *per se* is an effective means of in

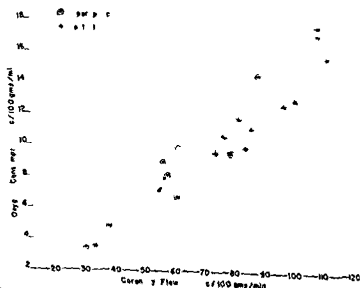


FIG 30 Graph showing relationship of oxygen consumption to coronary flow (Eckenhoff *et al* [?])

creasing left coronary inflow Hence in those instances in which the aorta was constricted peripheral to the coronary ostia the blood supply of the left heart was additionally increased by the elevated central coronary pressure For this reason the left heart will oper

ate it an advantage over the right heart in its ability to function with an increase in resistance load

When the coronary arteries are perfused at a constant pressure or with a normal pulsatile aortic pressure an increase in the venous return to the heart beating *in situ* augments the coronary flow mildly when aortic pressure is unchanged, and to a much greater extent when the aortic pressure is permitted to rise[3,23,35,46] Here as with increased resistance loads the increased coronary flow presumably results from augmentation of cardiac metabolism and its associated dilator mechanisms Eckenhoff *et al*[3] have shown that the coronary inflow response with increased blood pressure and cardiac output and work of the heart best follows the associated change in metabolism of the ventricle (Fig 50) However, it has been repeatedly shown in the denervated heart and heart lung preparation[3,5,75] that coronary arterial inflow or coronary sinus outflow is reduced or unchanged by alterations in cardiac output as long as the resistance against which the ventricles contract is unaltered If the preparation is innervated coronary flow increases with cardiac output[5] More recently however Katz *et al*[67] have concluded that the coronary flow increases with augmented cardiac output The explanation advanced is that the coronary vessels are passively dilated and their resistance to flow decreased as a mechanical adjustment to increased cardiac work and energy expenditure This concept, at present, lacks the necessary explanation of the physical mechanism by which an increased cardiac output without an increased aortic pressure can of itself cause passive mechanical dilatation of the coronary bed

Nervous Influences — The control of the coronary circulation by parasympathetic and sympathetic nerves has been the subject of much study For the most part the nervous influences on the coronary circulation have been studied by observing the coronary flow responses following electrical stimulation or severence of the nerves Although such procedures are not paralleled by normal occurrences in the animal, the observed responses are presumed to indicate the functions which the nerves are capable of exercising in the intact animal Further difficulty in interpretation results from the fact that the specific effects upon the heart muscle and on the coronary vascular system are largely experimentally inseparable and only the net effect can be observed Differences in methods and preparations are additional variables which may account for the discordant results of different investigators

According to different investigations, the vagus and sympathetic nerves contain both dilator and constrictor fibers (*See* reviews by Wiggers[35] and McDowall[73]) In general the so-called inhibitor and

constrictor fibers are said to predominate in the vagus while the dilator and accelerator fibers are found in the sympathetic nerves. The evidence for the constrictor effects has usually been the observation that abolition of the parasympathetic pathways in the heart lung preparation (by mechanical or chemical means) results in an augmentation of heart rate or coronary flow and stimulation of the peripheral ends of the cut vagi decreases coronary flow [4] In the fibrillating heart with the coronary arteries perfused with blood under a constant pressure vagal section and stellate stimulation usually decrease coronary inflow while vagal stimulation and stellate section usually increase coronary inflow [43] Hence in both the heart lung and fibrillating heart the normal presence of a tonic constrictor and inhibitor action is implied

None of these studies define the action of the vagi in the intact animal Section of these nerves or stimulation of their peripheral ends has never elicited any change in coronary flow as measured by the rotameter and orifice meter [41] and by the bubble flow meter [4] when blood pressure and heart rate are essentially unchanged However more recently Eckstein *et al*[5] observed a considerable decrease in coronary inflow (measured by a constant pressure meter) when the peripheral vagi were stimulated and in the presence of a somewhat lower blood pressure

Studies of action potentials and the effects of faradic stimulation of the sympathetic nerves to the heart indicate that they probably function in maintaining and augmenting the rate and vigor of the heartbeat [13 14 26 43 79] The findings that administration of acetylcholine to an atropinized heart causes the liberation of an adrenaline like compound [57] that stimulation of cardiac adrenergic fibers sets free an adrenaline-like substance [20] and that this is also normally present in heart extracts[87] all support this view

Stimulation of the stellate ganglia and/or their cardiac branches in the anesthetized open-chest dog increases mean flow in both right and left coronary arteries [43 79] This augmentation lasts for minutes and persists long after any heart rate or blood pressure change (if they occur) has returned to normal Figure 31 b illustrates a response in which the coronary inflow as measured with the rotameter was tripled the blood pressure temporarily rose and the heart rate was unchanged at 104 per minute Stimulation is also attended with extensive alterations in the coronary inflow patterns [4] The coronary inflow *patterns following* such stimulation (figure 31 b) are typical of experiments in which blood pressure and heart rate changed spontaneously In all experiments diastolic flow increases and systolic flow decreases with the latter becoming

largely back flow in other particulars the phasic flow response varies Examination of these curves indicates that, at least in part the net flow change (increase) may rest on a mechanical basis, for the duration of systole (in which the flow is decreased) is sharply reduced Thus at the same heart rate, the period of time occupied by diastole (in which the rate of flow is greater) is considerably increased However when allowance is made for this the residual flow increase is still considerable

The extensive alterations of inflow patterns with nerve stimulation are related to the influence of many complex and interdependent factors The pattern changes are regarded as the summated effects

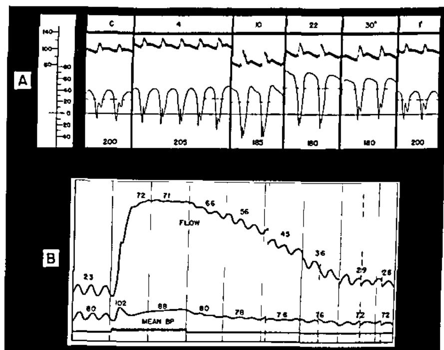


Fig 51 —Part A reproduction of a series of original pressure (upper) curves and rectified reconstruction (lower) of original velocity flow curves recorded in the descendens branch of the left coronary artery following stimulation of the left cardiac nerves Ordinate scales—pressure in millimeters of mercury on left flow in cubic centimeters per min on right Continuous horizontal line indicates zero flow level Interrupted line indicates mean flow level for each record segment Numbers on each record segment are At top time elapsed following beginning of nerve stimulation at bottom heart rate C control record Part B tracing of original record showing augmentation in mean blood flow as measured by a rotameter in the circumflex branch of the left coronary artery following a 2 minute stimulation of left cardiac nerves Numbers on curves cubic centimeters per min and millimeters of mercury Solid vertical intercepts 1 minute intervals At broken vertical intercepts recording stopped for ½ minute interval (Gregg and Shipley [45])

of alterations in some or all of these interrelated variables: vasomotor state, vessel elasticity, volume-elasticity coefficient, frictional resistance (viscosity effects), magnitude and rate of change of aortic pressure, extravascular compression (support), and rate of flow. These patterns and others are presented with the hope that subsequent studies will permit an adequate interpretative analysis.

The increased coronary inflow with stellate stimulation may occur with or without spontaneous elevation of blood pressure and also heart rate, or when the aortic blood pressure is artificially controlled and compensated to the control level. This indicates that the factors of heart rate and blood pressure and work are not indispensable to the natural mechanism through which the flow increase is mediated.

In no experiment with stimulation of the cardiac nerves from the stellate ganglia has coronary inflow been found to increase without gross visual evidence that the vigor of cardiac contraction increases or without experimental evidence of increased cardiac work and/or metabolism (Table 7). The mechanism by which the vigor of contraction is increased has not been identified. The possibility that adrenal secretion is responsible for the cardiac stimulating effect is largely discounted because (1) the cardiac response occurs within several seconds after initiation of stimulation, *which interval would* not appear to be sufficiently long for elaboration and transport of epinephrine from the adrenal gland; (2) the cardiac response is the same with or without the presence of intact adrenals.[79] Because of the promptness (one to three seconds) with which the heart responds it appears most likely that the physiological cause of coronary dilation and decrease in peripheral resistance in the coronary bed is a local one, perhaps *involving the release* of a myocardial stimulating substance at the endings of the stimulated nerves. Such a possibility is supported by the observations of Cannon and Rosenblueth[15,16,17] that an adrenaline-like substance (sympathin) is released in the heart when cardiac nerves are stimulated. However, regardless of the immediate effect of nerve stimulation on the myocardium, it is not improbable that the consequent increase in cardiac vigor and work and the accompanying increase in metabolism are largely responsible for the dilation of the coronary vessels and the observed increase in flow. In the light of present findings the cardiac nerves would appear to operate in conjunction with a mechanism by which the work output of the heart can be adapted to the requirements of the whole organism. The concomitant increase in coronary flow is regarded as a secondary phenomenon resulting from

TABLE 7 – THE EFFECT OF CARDIAC NERVE STIMULATION ON THE WORK AND METABOLISM OF THE LEFT HEART

Exp No	Mean Blood Pressure mm Hg		Coronary Flow cc/min		Cardiac Input cc/min		Work Changes KgM Work/min Left Ventricle		Condition
	Before	During	Before	During	Before	During	Before	During	
1	70	69			760	1087	0.72	1.01	Left cardiac nerves stimulated 2 minutes
	81	80	28	34	575	670	0.64	0.73	Right cardiac nerves stimulated 1 minute Flow in left circumflex
3	106	108	32	47	350	500	0.51	0.73	Left cardiac nerves stimulated 1 minute Flow in left circumflex
4	75	83	29	37	400	475	0.39	0.54	Left cardiac nerves stimulated ½ minute Flow in left circumflex

Metabolism Changes

Exp No	Heart Rate	Mean Blood Pressure	O_2 Content Vol %		A V O Difference	Coronary Inflow		Oxygen Utilization		Condition
			Art	Vent		cc/min	% increase	cc/min	% increase	
1	132	110	17.90	4.55	13.35	16		2.14		Control flow in left circumflex
	138	108	17.80	3.46	14.34	32	100	4.59	114	Stimulation left cardiac nerves [illegible] minutes
[illegible]	170	110	16.0	[illegible].98	13.02	17		2.21		Control flow in left circumflex
	1[illegible]0	110	15.7	[illegible].35	13.35	45	165	6.00	171	Stimulation left cardiac nerve for 2.5 minutes

coronary dilation occasioned by chemico-metabolic influences incident to the increased work and metabolism.

The experiments of Eckstein *et al* [58] offer evidence that the increase in the work of the heart is not essential to the associated increase in coronary inflow. Stimulation of the accelerator nerves in the open-chest dog produced an increase in vigor of contraction, cardiac output, cardiac work, coronary blood flow, and oxygen consumption. However, simultaneous nerve stimulation and inflation of a left auricular balloon to reduce the external work of the heart below the control value was likewise followed by increased vigor of contraction, increased coronary flow, and increased oxygen consumption. Thus the adrenaline-like substance released by nerve stimulation would appear to directly increase oxygen consumption. Whether a part of the increased flow arises from a direct effect of the substance on the coronary vessels cannot be told in these experiments.

The above observations and deductions do not exclude the possibility that cardiac nerves may exert a direct vasomotor influence on the coronary vessels, and previous investigators have interpreted the changes in coronary flow with nerve stimulation in terms of direct vasomotor influence on the coronary vessels. Experiments have been presented with the innervated fibrillating heart in order that changes in blood pressure, vigor of cardiac contraction, cardiac metabolism, and other variables could be excluded and the positive effects of nerve action on the caliber of coronary blood vessels observed.[63] Although both parasympathetic and sympathetic nerve stimulation caused significant alterations in coronary inflow, such experiments still fail to demonstrate conclusively that a direct vasomotor influence exists. The abolition of rhythmical contraction of the heart does not preclude the possibility that cardiac nerve stimulation can yet increase the vigor of fibrillary contraction and increase cardiac metabolism, thus establishing the primary response which could secondarily give rise to coronary dilatation.

It would seem most difficult to establish and identify conclusively by experimental means the separate effects of nervous influences upon the myocardium and coronary vessels because the physiological functions of these structures are so intimately related that their individual responses can be secondarily modified each by the other.

The Possibility of Reflex Control of Coronary Blood Flow.—A proper demonstration depends on the observations that the vagus and sympathetic nerves to the heart are tonically active as far as coronary blood flow regulation is concerned or can be made so by the induction of adequate stimuli arising either within the heart or peripherally.

For the functioning of intracardiac reflexes, a case has been built up based on the findings in the heart lung preparation. In the innervated heart lung preparation, vagus section increases coronary flow, and in the same innervated preparation, increased cardiac output increases coronary flow, but this effect is abolished after vagal section[5]. Control via the sympathetic nerves has not been reported in this preparation. However, in the anesthetized dog an increase in cardiac output increases coronary flow with or without intact vagi[35,45] when the coronary arteries are perfused at a constant pressure (constant pressure flow meter) or with a pulsatile aortic pressure (orifice meter).

Ligation of a coronary artery has been reported to lead to reflex coronary vasoconstriction in the other coronary artery which has led to fatal ventricular fibrillation[70]. During a number of years the author has accumulated experiments in which the flow was measured in a coronary artery or in the coronary sinus when a second coronary or its branch was ligated or occluded in the anesthetized dog. No evidence of the operation of such a reflex was ever obtained in this preparation. On the contrary, in 7 experiments selected at random of which 2 were previously published[60] 18 of 19 determinations showed that following occlusion of the common left or the left descendens the flow in the right coronary increased considerably, while when the right coronary was ligated left coronary flow rose (Table 8). It is believed that these flow augmentations

TABLE 8.—THE QUESTION OF REFLEX CONSTRICTION OF THE CORONARY VESSELS

Mean Aortic Blood Pressure mm Hg		*Coronary Arterial Inflow cc/min*		*Coronary Venous Outflow cc/min*		*Condition*
Before	*During*	*Before*	*During*	*Before*	*During*	
		Common Left		Cor Sinus		
78	78	45	47	34	3[illegible]	Right coronary clamped
		Rt Cor		AC Veins		
9[illegible]	90	12	12	4.0	4.5	Left descendens clamped
93	93	14.0	16.0	9.2	7.4	Common left clamped
92	92	12.0	15.0	13.0	11.0	Common left clamped
75	75	11.5	13.5	4.4	4.0	Common left clamped
		Rt Cor		Cor Sinus		
8[illegible]	85	8	12.5	55.0	2.0	Common left clamped
105	105	13.0	15.0	63.0	3.0	Common left clamped
65	65	9.0	13.0	36.0	3.0	Common left clamped

arise from an anatomical and functional overlap of the right and left coronary arteries in the two ventricles. These results have been confirmed[24,77]. In such preparations the effect of anesthesia and in some cases the cutting and ligating of the artery in which the flow change is to be measured constitute extensive deviations from

a normal nerve state. That such results necessarily represent the events that would occur if the animal were unanesthetized and in a normal state cannot be accepted.

Changes in coronary blood flow which might result from extracardiac stimuli would be of great clinical interest and their demonstration might aid in elucidating the mechanism of the relationship between angina pectoris and its various incitants such as eating, abdominal distention, cold and exercise. The claim is made that many diverse afferent stimuli affect the coronary flow. For example, stimulation of many afferent nerves,[39,40,56] distention of the stomach, gall bladder and esophagus,[56] exercise[40] and cutaneous pain[33] all are presumed to increase coronary sinus flow in the anesthetized dog, while elevation of cerebral blood pressure and carotid sinus pressure[54] decrease coronary flow in the innervated heart lung preparation. In addition, there are various experiments with the direct current thermostromuhr in the unanesthetized dog in which digestion and exercise increase coronary flow[7,35,37] and cold stimulation of the mucous membranes decreases coronary flow,[31] whose interpretation is difficult due to the known technical limitations of this type of flow recorder. In the former instance, although the magnitude of the flow change is generally small, yet the directional trend could be correct. However, in none of these experiments were the recording device and data sufficient to establish that *no changes* occurred in heart rate, cardiac output, blood pressure, length of systole and diastole, each of which could alter cardiac metabolism, work and/or coronary flow. Actually, the experiments of Eckenhoff *et al.*[24] with the bubble flow meter indicate that with increase in intrabiliary tension the coronary flow response was variable and always in the same direction as the blood pressure change. It is therefore unreasonable to maintain, as has been done, that such agents have caused active vasoconstriction or vasodilation in the coronary bed and that such changes are necessarily largely controlled through nervous reflexes. This is especially so since in each experiment the effects of the stimuli were not tested after as well as before cutting of the cardiac nerve fibers.

Heart Rate. – The evidence is conflicting, and no definite statement can be made concerning its effect on coronary blood flow. With the dog's heart beating *in situ* at an essentially normal rate, augmentation of heart rate increases left coronary inflow mildly when the rate increases spontaneously,[4] but does not change when the hearts are electrically driven.[41] In more simplified preparations (heart lung or isolated heart of the dog) and with hearts electrically driven, increase in heart rate in the middle range does not affect

coronary outflow, and with the more rapid rates coronary outflow decreases.[1, 3, 5, 54]

The explanation of these differences is not apparent, for the necessary information is not available. On purely mechanical grounds at least two factors operate to control coronary inflow in the presence of a changing heart rate. Augmentation of heart rate would decrease coronary flow per minute because it substitutes more periods of low flow, *i.e.*, systole, for portions of periods of higher flow, *i.e.*, diastole. In addition, systolic flow per beat would be less as the result of shortening of systole and the increase in systolic peripheral resistance. Hence, the minute flow would be decreased through reduction in both systolic and diastolic flows. However, the situation is complicated by the fact that changes in heart rate may alter the vasomotor state of the coronary bed and hence coronary flow by shifts induced in the metabolism and work of the heart and by the possible operation of intra- or extracardiac reflexes. No studies are available on these potentially important controlling factors.

Temperature and Blood Viscosity.—In the intact dog diathermy over the precordial region sufficient to raise the temperature of the right ventricle from 96.2 to 104° F. was without significant effect on coronary sinus flow.[7] However, in the dog heart-lung preparation and isolated, revived, and perfused human heart in which heart rate was controlled, the coronary flow increased as the temperature of the perfusion fluid decreased.[8, 65, 5]

Since viscosity of the blood contributes considerably to the resistance in any vascular bed, changes in it should alter the volume of coronary blood flow. However, there are no critical experiments reported in which the effect of viscosity *per se* has been quantitated. When the heart is perfused with a constant pressure flow meter first with blood and then with Locke's solution, the minute volume of coronary flow increases 3 to 4 times with the flow increase occurring in both systole and diastole.[4] However, in this instance, anoxia could well have been a contributing factor.

Valvular Lesions.—As previously indicated, pulmonary and aortic valve stenosis by constriction of the pulmonary artery and aorta (between the aortic valves and the coronary ostia) increases considerably mean coronary flow in both coronary arteries and both the systolic and diastolic flows in the anesthetized dog provided the aortic pressure is fairly well maintained. These are the immediate and acute flow effects. This augmentation of flow is invariably associated with an increased metabolism of the respective ventricle and could well be the early response in the human to gradual and mild stenosis of the corresponding valves.

No pertinent experiments are available concerning the effect of mitral stenosis on coronary flow. With aortic insufficiency systolic flow increases and diastolic flow decreases.[19,36] The net change in cyclic flow depends on the relative alterations in systolic and diastolic flow which in turn depend on the severity of the lesion (Fig. 52). Since the metabolism and work of the hearts in the presence of this lesion were not known, interpretation of the experiments in terms of coronary flow determinants is difficult.

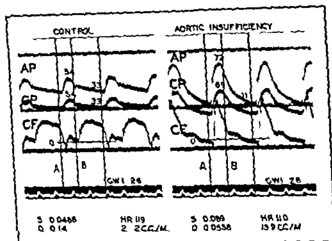


Fig. 52.—Reproduction of original record showing the effect of aortic insufficiency on phasic and mean blood flow in the ramus descendens anterior. Horizontal line, zero flow; vertical lines A, B, end of diastole and systole. AP, aortic pressure; CP, coronary pressure; CF, coronary flow. Time 0.2 sec. (Green and Gregg.[19])

Shock.—In standardized hemorrhagic shock in dogs, after infusion of the previously withdrawn blood and restoration of the pre-shock blood pressure level, coronary inflow is increased for a considerable period of time.[78] This signifies a decrease in peripheral coronary resistance whose early manifestation can in part arise from the anoxia during the hypotensive period, but the mechanism for the sustained effect cannot be told in these experiments.

Summary.—A major consequence of the normally very low oxygen content of the coronary venous blood (2 to 6 volumes per cent) is to throw an inordinate responsibility on the volume of coronary blood flow in meeting an increased demand of the heart for oxygen. In the situations in which it has been measured, the two ventricles have been found to have at their disposal a compensatory mechanism by which their coronary blood supply can be increased and con-

least in part, be adjusted to their energy requirements It is believed that an increase in metabolism (increased oxygen demand) and/or decreased supply of oxygen (anoxia) are the primary antecedents which indirectly give rise to coronary dilation and an increasing coronary flow This is supported by the experimentally demonstrated facts, (1) that an augmented load of either ventricle increases the work and metabolism of the respective ventricle, (2) the failure to obtain an increased coronary flow response with cardiac nerve stimulation without evidence of increased cardiac vigor and metabolism, the lack of conclusive evidence that the cardiac nerves have a direct vasomotor influence and the observation that cardiac metabolism is considerably increased (3) that progressive anoxia gives rise to a large increase in coronary flow This thesis that the coronary flow is automatically adjusted to the requirements or products of metabolism of the heart has been more recently amplified and a more precise validation placed on it

As far as can be ascertained, this coronary flow response has its origin within the heart but the exact identity of the mechanisms involved (chemical or nervous) is unknown Since various supposed normal products of metabolism oxygen lack and coronary ischemia dilate the coronary vessels and increase flow presumably no one chemical agent is responsible The effect is more likely to be the simultaneous and summated effect of all the demands on and the products of cardiac metabolism

THE PROBLEM OF DRUGS

The pertinent literature has been reviewed by Smith [83] Green [34] and Jochim [59] The effects of and the mechanisms of action have been studied in the isolated heart fibrillating heart heart lung preparation and heart *in situ* It is not believed that these studies are significant except with the heart *in situ* for not only can a drug have different effects on the hearts of two different preparations, but also many of the drugs have extracardiac effects on pulse rate and the metabolism of other organs on respiration and other activities of the body which may in themselves so alter the cardiac load or coronary vasomotor state as to overshadow the local coronary effect

Drugs may be effective in changing the myocardial blood supply through alteration of the blood pressure and/or vasomotor state of the normal and collateral coronary vascular channels In addition certain of the drugs alter blood flow by modifying the vigor of cardiac contraction Through lack of adequate methods great confusion

still exists as to the mechanism of drug action and in most instances, no definite statement can be made

It is a simple matter to determine experimentally whether a given drug increases or decreases coronary flow with the heart *in situ*. Khellin, papaverine, the nitrites, xanthines, acetylcholine, epinephrine, paradrine, coramine, histamine all increase coronary flow, while pitressin decreases coronary flow. It has been argued that when with a given drug coronary flow increases considerably in the presence of an unchanged central coronary pressure the coronary bed may be said to have undergone active dilatation. However, this does not indicate the drug to use, for there may be associated with the active dilatation an increase in extravascular support and metabolism so that the increase in blood flow may not have been obtained so cheaply, after all. While such comparison has proved useful from an experimental point of view, neither it nor any other method has enabled experimenters to estimate separately the determinants of coronary flow, and hence to decide whether any particular drug is the one of choice.

In the following, it is obvious that just what alterations in coronary flow determinants in the heart and in the extracardiac vascular system cause an increase or decrease in flow has never been fully determined for any drug. Actually, most drugs have never been tested with the heart *in situ* for their coronary flow effect. In addition, the testing of drugs with the heart *in situ* has been limited to the left coronary artery.

Pitressin.—Of the drugs used clinically, pitressin is the only one which decreases coronary flow by all methods of study, and increases the total peripheral resistance to flow, that is, flow decreases in the presence of an increased central coronary pressure.[34,37,55,56] Figure 53 illustrates the sustained characteristic reduction in coronary inflow which occurs throughout the cardiac cycle following its injection into a coronary artery. It is believed that this drug acts by direct effect on the coronary arterioles, but a decrease in cardiac metabolism and vigor of contraction or an increase in extravascular support have not been ruled out as the cause of the flow decrease.

Nitrites and Xanthines.—These studies include observations on the inflow into coronary vessels perfused under a constant pressure, on the outflow from the coronary sinus and/or pulmonary artery of perfused quiescent beating and fibrillating hearts, on the coronary arterial inflow under constant or declining pressure in the heart lung preparation or whole animal, on the coronary sinus outflow in the heart lung preparation or whole animal, and on the phasic flow in the anesthetized dog by the orifice meter and mean flow in the left

coronary artery by the nitrous oxide method These drugs increase coronary flow by nearly all methods of study and in nearly all preparations [11, 1, 34, 8] The fact remains, however, that alterations in coronary blood flow in the intact animal may differ significantly in extent and even in direction from what would be anticipated as a

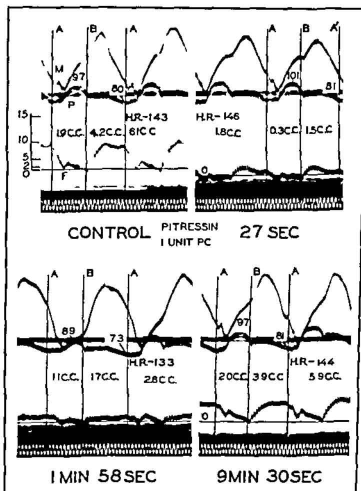


FIG 53 —Reproduction of a series of record showing effect of pitressin injection into the ramus descendens anterior Upper curve myogram middle curve aortic pressure lowest curve phasic coronary inflow with orifice meter Time 0 02 sec (Green *et al* [37])

result of active changes in the size of the coronary vessels because of varying degrees of extravascular compression by the contracting cardiac muscle, changing cardiac output (mechanical reflex and metabolic effects), and alterations of blood pressure

Figure 54 illustrates the changes in phasic coronary inflow following injection of sodium nitrite into the left coronary artery This

response is typical of the other nitrites Since the flow increases largely in both systole and diastole and in the presence of a decreased central coronary pressure and with a constant heart rate and only a slight decrease in the S/D ratio the conclusion is inescapable that [illegible]

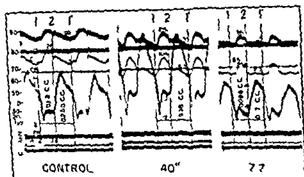


FIG 54 —Reproduction of segments of a record showing the effect on blood pressure and phasic left coronary inflow of injecting 3 mgm sodium nitrite into the left coronary artery AP aortic pressure CP central coronary pressure FL phasic left coronary inflow cc on flow curves flow per beat in systole and diastole horizontal lines zero flow First record control second and third records 40 sec and 7 7 min after injection of drug Time 0 02 sec (Boyer and Green [12])

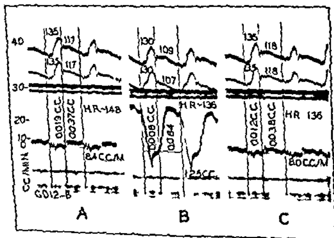


FIG 55 —Reproduction of segments of record illustrating the effects of left intracoronary artery injection of 5 mgm of Theamine (theophylline monoethanolamine) A control B 90 sec after injection C [illegible] 8 min after injection top curve aortic pressure middle curve coronary pressure bottom curve phasic coronary inflow with orifice meter Fine horizontal lines zero flow cc on curves flow per beat in systole and diastole and total flow per min Vertical lines separate systole and diastole Time 0 02 sec (Boyer and Green [illegible])

coronary artery by the nitrous oxide method. These drugs increase coronary flow by nearly all methods of study and in nearly all preparations.[31, 34, 8] The fact remains, however, that alterations in coronary blood flow in the intact animal may differ significantly in extent and even in direction from what would be anticipated as a

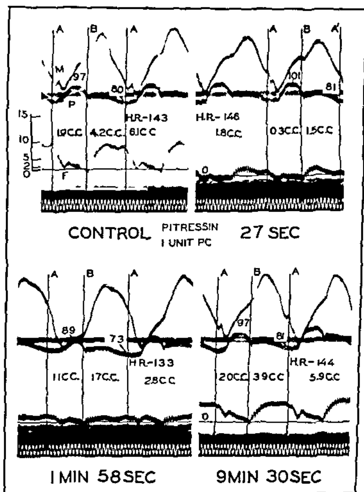


FIG. 53.—Reproduction of a series of records showing effect of pitressin injection into the ramus descendens anterior. Upper curve, myogram; middle curve, aortic pressure; lowest curve, phasic coronary inflow with orifice meter. Time 0.02 sec. (Green *et al*.[37])

result of active changes in the size of the coronary vessels because of varying degrees of extravascular compression by the contracting cardiac muscle, changing cardiac output (mechanical, reflex and metabolic effects) and alterations of blood pressure.

Figure 54 illustrates the changes in phasic coronary inflow following injection of sodium nitrite into the left coronary artery. This

This initial flow augmentation might then indicate a direct dilator action on the coronary vessels although even here an early metabolic influence cannot be ruled out. At all events, with the larger doses most of the coronary flow increase can be due to the large increase in cardiac metabolism.

Acetylcholine intra-arterially increases coronary blood flow in the dog in the fibrillating heart,[56] heart-lung preparation,[1] and in the anesthetized dog.[4] If the dose is properly chosen, this response in the beating heart occurs without a significant change in blood pressure or heart rate. The increased flow response is completely abolished after atropine. This drug then increases the mean bore of the coronary vessels since the flow is elevated in the presence of a

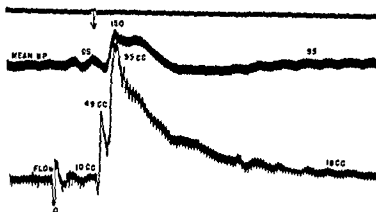


FIG. 56.—Reproduction of record showing effect of intracoronary artery (left descendens) injection of epinephrine on mean aortic pressure and mean left coronary artery inflow as measured with the rotameter. Arrow, time of injection. Time, 2 sec. (Shipley et al.[49])

normal or lower central coronary blood pressure. The effect of this drug on cardiac metabolism has not been determined and whether its flow effect is directly on the intrinsic smooth muscle of the coronary vessels or is induced through metabolic changes of the heart is unknown.

Opiates.—Few studies have been made of the action of morphine and its derivatives on the coronary circulation. Papaverine increases left coronary inflow in the anesthetized dog[23,30] while the blood pressure and heart rate may be unchanged or the former decreased. Figure 57 illustrates a typical mean flow response to left coronary artery injection of the drug as recorded with the rotameter. The cardiac work and metabolism are stated not to be increased by

this group of drugs exerts a vaso-dilating action on the coronary vessels [1] This could arise from a direct effect of the drug on the coronary vessels, although a change in cardiac metabolism and work (decrease) cannot be ruled out as the cause of the flow increase

With the xanthines the mean flow is increased the net result of a marked increase during diastole and a decrease during systole which occurs in the presence of a normal or mildly altered blood pressure and without significant change in cycle length or S/D ratio [1, 34] Usually, the heart shows increased vigor and its metabolism and work are increased [9] Under such circumstances it is not justifiable to attribute vasodilation solely to the action of the drug for the increased vigor of contraction can, of itself, through increased liberation of metabolites be *partially, if not wholly, responsible for the* vasodilation A typical flow response following injection of Theamine into the left coronary artery is shown in figure 55

Epinephrine and Acetylcholine —Since the generally accepted theory of autonomic nerve transmission is based on the liberation of acetylcholine and epinephrine like substances the coronary flow effects with these agents are of particular interest in connection with coronary innervation

The action of epinephrine on the coronary blood flow has been investigated more extensively In most dog preparations including the fibrillating heart [66] heart lung preparation [71] and heart beating *in situ* [4, 37, 80] intracoronary artery injection of epinephrine increases coronary blood flow In the latter preparation its effect on the coronary flow pattern is similar to that obtained during *stimulation* of cardiac accelerator nerves (Fig 51) There is also an associated increase in cardiac metabolism and in vigor of contraction [71] The flow increase may be regarded as the net effect which results from *an augmented* extravascular support tending to decrease flow a metabolic dilator effect tending to increase flow and whatever direct dilating effect epinephrine may have at the time on the coronary arterioles It is difficult to determine the respective magnitude of each separate effect Regarding its dilating effect *per se* on the coronary vessels, the evidence is conflicting Green *et al* [37] found that following injection of epinephrine into the left coronary artery the coronary flow increased simultaneously with elevation of blood pressure and increased vigor of contraction while Shipley and Kohlstedt[80] indicate *that this is preceded by a transient period* of flow increase without change in blood pressure (Fig 56) In the small dose range (0 02 to 0 2 micrograms) a significant increase in coronary flow is seen without change in heart rate or blood pressure which indicates a significant dilator effect on the coronary vessels

substantiate the original findings [18] and reinfusion of oxygenated coronary sinus blood does not augment coronary flow

Of the remaining drugs used in heart disease (coramine pilocarpine atropine metrazol nicotine) studies of their action are insufficient to warrant a statement as to the mechanism of their effect on the state of the coronary bed In addition the effects of glucose and insulin and various electrolytes (sodium chloride calcium chloride calcium gluconate potassium chloride magnesium sulphate) have been studied generally in the fibrillating heart in abnormally high concentrations and hence the findings do not permit interpretation

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this drug [9] The effect of morphine on coronary flow is not known

Digitalis —The use of digitalis and its allied compounds in the treatment of coronary artery disease would be ill advised if the drug decreased coronary flow and constricted the coronary vessels No data are available by an acceptable method as to its effect with the heart beating *in situ* Its effect *studied in other preparations* is variable and inconclusive

Other Drugs —Quinidine is apparently without effect on coronary flow, although it has never been tested with the heart *in situ*

Extracts of seeds of Ammi Visnaga Lam (Arabic Khella), an umbelliferous plant growing wild in the Eastern Mediterranean regions have been used by the local population since ancient times as an *antispasmodic in renal colic and ureteral spasm* *A fresh interest in* khellin arose as the result of the discovery that, orally or intravenously, it acts for many hours as an extremely potent coronary vasodilator in the heart lung preparation and in the heart *in situ*, and

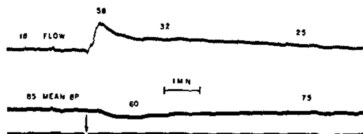


Fig 57 —Reproduction of record showing effect of the injection of 5 mgm of papaverine into left coronary artery on mean aortic pressure and mean left coronary flow as measured with the rotameter (Shipley *et al* [80])

which, in the doses used has no effect on the general blood pressure and does not increase the oxygen requirements of the heart, *i e* it *acts only to relax the intrinsic smooth muscle of the coronary arterioles* [6 10] Reports from its use for the relief of angina have been encouraging [7] However *Foltz et al* [9] *did not find that it increased* coronary inflow in the anesthetized dog

Brief mention should be made of histamine Although it is not used therapeutically in heart disease interest in the compound stems from the idea that it or a histamine like substance is present in all coronary venous blood and that it is the main natural coronary dilator [8] In dog preparations it increases coronary inflow in the presence of a normal *or decreased blood pressure* *The significance* of this dilator effect is not known for repetition of the work indicating that it is a normal constituent of coronary venous blood does not

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pensed with and the heart blood passed through a specially devised oxygenation apparatus.[6,30,61] To more nearly approximate the normal physiological environment, the heart and lungs may be removed in such a way that the cerebral circulation remains connected to the heart, and the vagal and sympathetic nerves of the heart remain intact.[36,37]

With the heart beating *in situ*, the energy output is calculated from the same formula but expressed somewhat differently:

Energy = coronary flow $\times$ coronary O_2 A-V difference $\times$ 2.057

As indicated in the above formula, the oxygen consumption of a ventricle is calculated from the product of its coronary arteriovenous oxygen difference and the blood flow through its coronary artery. The arterial sample can come from any convenient artery. The coronary venous sample for the left heart must come from the coronary sinus and is readily obtained by insertion into it of a catheter via the antecubital or jugular vein in the unanesthetized or anesthetized dog or human,[3,41,83] or by insertion of a cannula in the open or closed chest dog.[45,57] For the right heart, the coronary venous sample *must* come from anterior cardiac veins.[60] Since these veins are very small, blood samples can be obtained only by their cannulation through the right atrium in the open-chest animal. The coronary flow is determined either by measuring left and/or right coronary inflow by one of the appropriate methods already indicated or, *for the left ventricle*, by measuring flow through the coronary sinus and multiplying by a factor to obtain total coronary inflow for the left coronary artery.

In practice, the method of indirect calorimetry is beset with difficulties. Certain general criticisms apply to it and the interpretation of the results by this method must be tempered by certain underlying assumptions. The anaerobic and aerobic processes in the myocardium must be in equilibrium over the time of measurement, *i.e.*, there can be no oxygen debt. Actually, no measurements exist to establish whether this equilibrium does or does not exist in the normal heart or in a state of failure. In addition, a fixed caloric value for oxygen is also assumed from which the work equivalent of oxygen (as used in the above equation) is *computed*. Since the type of substance oxidized affects this value and this is difficult to determine accurately, a maximum error of 5 per cent is possible.

Certain of the difficulties are particularly applicable to the heart beating *in situ*. (*1*) If left coronary inflow is established by quantitation of coronary sinus flow (times a factor), the assumption is made that the quantity of blood draining through the coronary sinus is a constant fraction of that which enters the left coronary artery.

Chapter 7

METABOLISM AND WORK

As indicated in the previous chapter, coronary flow generally varies with the level of cardiac metabolism. However, to understand properly the functioning of the myocardium its metabolism, output, and work must be precisely and simultaneously determined. From a consideration of the methods which follow, it is apparent that this has been a most difficult task and has not been fully realized.

METHODS

Energy Output and Oxygen Utilization.—The total potential energy degraded by the heart can be quantitated either directly by physical measurements of heat loss, or indirectly by chemical measurements of the underlying metabolism.

The physical methods have not been extensively applied to cardiac metabolism. Microcalorimetry has been used to measure total heat production in the frog heart,[8] and heat production has been measured in muscle strips. The latter may be used to indicate factors which may alter the rate of metabolism, but the data can have no bearing on the actual level of oxidation existing when the heart is in a normal environment. In the method of polarography, which has been applied successfully to the quantitation of brain metabolism, a bare platinum wire is thrust into the tissue and, by its connection to a salt bridge and suitably adjusted voltage, it is possible to record the oxygen tension of the tissue *in vivo* as a function of the amperage.[56] This method might also be applicable to the heart provided electrode difficulties induced by cardiac movements could be eliminated.

The method of indirect calorimetry has been intensively applied to the study of cardiac energetics. In this, the energy output of the heart in potential kilogram meters of work per minute is calculated from the formula

$$Energy = Oxygen\ usage/min \times 2.057$$

in which 2.057 is the energy equivalent of 1 cc. of oxygen in kilogram meters.

In the simplest preparation, the energy output of the heart in a heart lung preparation[49] is determined by measuring the oxygen usage by means of a metabolism apparatus connected directly to the trachea of the preparation. The metabolism of the lungs may be determined separately and deducted,[5] or the lungs may be dis

blood ejected in grams and g = 9.8. The mean velocity (V) during systolic ejection in centimeters/second at the root of the aorta or pulmonary artery is calculated from

$$V = \frac{\text{systolic discharge per beat}}{\text{cross-sectional area in sq cm at aortic or pulmonary root} \times (F)}$$

in which F is duration of ejection. Since the cross sectional areas of the aorta and pulmonary artery are presumed to be equal, the kinetic factor is assumed to be the same for both ventricles.

In the normal human heart when the heart rate is 70, systolic discharge 60 cc, aortic (and pulmonary artery) diameter 2.5 cm, duration of ejection 0.30 sec, mean aortic blood pressure 100 mm Hg, mean pulmonary artery pressure 20 mm Hg, the work of both ventricles is about 7.0 kg meters/min. This is calculated as follows:

Velocity (left or right) $= \frac{60}{(0.30)(4.9) \times 100} = 0.41$ meters/sec

QR (left) $= 60\ (0.10)\ (13.6) = 81.5$ gram meters/beat

QR (right) $= 60\ (0.02)\ (13.6) = 16.3$ gram meters/beat

$\frac{wV^2}{2g}$ (left or right) $= \frac{60\ (0.41)^2}{2\ (9.8)} = 0.515$ gram meters/beat

Total work/beat $= 81.5 + 16.3 + 0.515 + 0.515 = 98.8$ gram meters

Work/min $= \frac{98.8 \times 70}{1000} = 6.92$ kgm meters

Although the systemic and pulmonary artery pressures can be readily obtained and directly recorded by arterial puncture or by catheter technique, the accuracy of the determination will depend largely on the accuracy of the particular method for cardiac output and, in part, on the values for the internal bore of the pulmonary artery and aorta at the pulmonary and aortic valves. In the absence of certain knowledge of the effective diameters of the aorta and pulmonary orifices in the human heart during life, both of which must vary with the pressures within them, it is not possible to make reliable calculations regarding the work done in giving velocity to blood since this work is inversely proportional to the square of the diameter of the outlet.

This warrants further investigation,[49] (2) although essentially all the blood draining into the coronary sinus in the anesthetized dog comes from the left coronary artery it does not follow that the oxygen content of the coronary sinus blood is representative of that draining the left ventricular myocardium since only a fraction *(70 to 80 per cent) of left coronary artery inflow drains through the coronary sinus* By catheter sampling, the blood obtained from the coronary sinus may not all arise in the myocardium Some may come from the right atrium or from the fatty tissue of the heart draining into the coronary sinus However contamination from the right atrium can be prevented by using a catheter with an inflatable balloon in the sinus,[57] or by tying a catheter or cannula into the coronary sinus[4] or great cardiac vein[50] in the open or closed-chest dog, and permitting the blood to feed into a convenient peripheral vein or right atrium when not being measured (3) while contamination in the AC veins by retrograde flow from the right atrium is not possible because of the method of sampling the adequacy of such a sample to indicate coronary venous oxygen saturation in the right heart is questionable, since the fatty tissues of the right heart may drain by this pathway and the oxygen content of the AC veins is not representative of blood draining the coronary bed of the right ventricle Actually much of the blood in the AC veins *arises from the left coronary artery*, as well as the right coronary as already indicated and the oxygen content of these two sets of superficial veins is often different

Cardiac Work —The portion of the energy output of the left ventricle that appears as work can be roughly calculated from the product of mean aortic blood pressure and cardiac output The work done by the right heart can be similarly calculated except that the *mean pressure is that in the pulmonary artery* Such calculations assume that the velocity factor constitutes but a very small part of the work of the heart Normally this is in the order of 1 to 2 per cent However when the cardiac output is quite large in the presence of a decreased systemic pressure or especially if aortic or pulmonary stenosis occurs the kinetic factor can approximate up to 50 per cent of the total cardiac work [6] For a somewhat more *precise evaluation of the work done by either ventricle* the following formula may be used

$$W = QR + \frac{wV^2}{2g}$$

in which W is work in gram meters/beat Q is cardiac output in cc/beat, R is mean aortic blood pressure in meters Hg w is mass of

determined Whether in man the pulmonary artery gives a more representative sample of mixed venous blood as compared to the right ventricle or atrium is still under consideration

Curiously enough except for some old experiments[9] the Fick procedure itself has never been checked against direct flow measurements While the soundness of the Fick principle cannot be denied, its adequacy under the necessary experimental conditions and environment has never been determined Experiments have been performed in the author's laboratory in which the cardiac output as determined by the Fick procedure in the anesthetized closed or open-chest dog has been compared with the cardiac input or output as obtained with an optically recording rotameter inserted into the venae cavae, pulmonary artery or aorta[84] For the more accurate determination the catheter for sampling mixed venous blood must be at or beyond the pulmonary valves or a progressively increasing error will occur as the catheter tip approaches the right atrium With wide ranges of cardiac output and systemic oxygen arteriovenous differences prevailing the flow values compared favorably especially with the rotameter in the pulmonary artery the only site where total cardiac output including the coronary flow has been directly measured Here 9 of 10 comparisons agreed within less than ± 8 per cent which is within the range of known technical inaccuracies

Cardiac Efficiency —Since it is known that the usage of 1 cc of oxygen liberates energy equivalent to about 2.057 kilogram meters of work it is possible by measuring the oxygen used and the work actually done by the heart to find out what proportion of this energy expenditure appears as work The remainder is presumably lost as heat This ratio of work done to energy set free the mechanical efficiency varies greatly in the mammalian heart Values have been obtained in the isolated heart to the intact human heart under a great variety of conditions

RESULTS

Oxygen Extraction —The oxygen extraction values for the blood vessels of the left and right heart of the dog *in situ* under different dynamic conditions are suprisingly high Some of the data obtained in the author's laboratory and by others are indicated in Table 9 The oxygen extraction from the left coronary artery ranges from 7.8 to 15.2 volumes per cent and has a similar range in the unanesthetized dog[83] anesthetized open or closed-chest dog[41, 46, 47] and in the normal human with a catheter in the coronary sinus[3] In the

Cardiac Output —Numerous devices and procedures are available for the determination of cardiac output or cardiac input in the anesthetized dog A plethysmograph can be put over the ventricles and their change of volume during contraction measured by some form of optical or mechanical recorder, or a flow metering device can be inserted into the circulation For the latter, a mechanical stromuhr [33] Pitot tube, [4] or rotameter[48] may be inserted into the aorta, pulmonary artery, or venae cavae to measure flow [86] In addition, the venae cavae can be cut in the open-chest dog and allowed to bleed into the chest cavity, and the blood is then pumped mechanically (after metering) into the right heart [0] Of these, only the rotameter has been used to measure cardiac output in association with studies of the coronary circulation While much valuable information has been obtained from such methods, they indicate only what the heart does under the handicap of anesthesia and traumatic surgery and do not furnish information as to what the heart does under more nearly normal *conditions*

A number of other methods have been applied to both unanesthetized animals and man Measurements of cardiac output have been made using the dilution principle [55 56 91 99 101] the pulse pressure [54 6] *x* ray electrokymograph,[1 60] ballistocardiograph,[90] and capacitance[100] methods, and also by the principle that cardiac output equals the rate of uptake (or output) of some substance by the body divided by the arterio-mixed venous blood difference of the substance Of these, the Fick procedure [34] which is a variation of the latter procedure, has been brought to a high degree of perfection This constitutes the only method that has been used in conjunction with simultaneous measurements of the coronary circulation In this the oxygen consumption arterial oxygen content (any convenient artery) and mixed venous oxygen content (by right heart or pulmonary artery catheterization) are determined Thus an individual who uses 300 cc oxygen per minute with an oxygen arterio mixed venous *difference of 5 cc /100 cc blood will require 6 liters of blood* per minute to deliver this oxygen to the tissues Since the blood gas concentration remains constant the experimental procedure has no time limit Usually the blood samples are withdrawn at a steady rate for a fraction of the time that the oxygen usage is measured and then analyzed for oxygen content By passing the blood over a photoelectric cell as it is withdrawn, its per cent oxygen saturation[53] has been continuously recorded Simultaneous registration of the moment-to moment changes in the oxygen concentration in the arterial and venous samples together with the slope of the oxygen usage curve, should enable the cardiac output to be continuously

TABLE 10.—Comparative Values for Coronary Flow, Cardiac Metabolism, Work and Efficiency in Different Preparations

Author	Preparation	Method: Coronary Flow	Method: Cardiac Output	Mean B.P. mm Hg	Per 100 gm Left Ventricle per Minute: Cardiac Output cc	Work Kg Meters	L. Cor. Flow cc	O_2 Used cc	Total Energy Kg Meters	Efficiency
Green et al [a]	Open-chest dog	Rotameter; Nitrous oxide		101; 1[illegible]0; 95	1 90	–.05	7; 91			
Sealy et al [44]	Open-chest dog		Rotameter (pulmonary art.)	118	6 0	4 3	80	10 0	21 9	19 6
Harrison et al	Open-chest dog	Morawitz cannula; Nitrous oxide	Fick	133; 138	4340; 4[illegible] 0	7 9; 7 1	74; 71	9 6; 9 7	10 8; 0	40 0
Eckenhoff et al	Anesthetized dog; Anesthetized dog	Nitrous oxide	Fick	115						
Goodale et al	Unanesthetized trained dog		Fick	119	[illegible]700	12 45	151	10 5	40 –	31 0
Blalock et al		Nitrous oxide						8 0	16 4	11 0
Spencer et al	Unanesthetized trained dog			1[illegible]; 100	1[illegible]0; 1300	1 8; 1 8		4 [illegible]	9 3	10 3
Lauson et al [26]	Heart-lung				41 0	5 5	65	[illegible] 8	16 0	[illegible]3 0
Gollwitzer-Meier and Kramer [a]	Heart-lung		Fick	97	[illegible]8 0	3 4				
Cournand et al	Normal Human	Nitrous oxide	Fick	9[illegible]	4000	4 0				
Bing et al	Normal Human; Normal Human L. Vent.		Fick	84	8000	1 4				
Riley et al	Normal Human Rt. Vent.		Fick	13						

* Data only partially extracted from indicated source to show trends. In some instances data for above columns not available in original work. For these, approximate calculations made as follows: For the dog, weight of left ventricle estimated on basis heart wt./body wt. = 0.00[illegible]8, left ventricle/body wt. = 0.00369 (see Herrman, G. R., Am. H. J. 1: 213, 1926). For the human, weights of left and right ventricles calculated on basis heart wt./body wt. = 0.00[illegible] (see Smith, H. L., Am. Heart J. 4: 9, 1928). Blood pressure for (4) (14) assumed.

TABLE 9.—CHEMICAL CHANGES IN THE CORONARY BLOOD

Author	Condition	O_2 Capac Vol %	O_2 Content Vol %				CO Content Vol %		R Q	Lactate mgm %		Glucose mgm %		Pyruvic Acid mgm %	
			Art	Cor Vein	A V Diff	Mixed Venous	Art	Cor Vein	Cor	Art	Cor Vein	Art	Cor Vein	Art	Cor Vein
Gregg et al [4]	Anesthetized closed chest dog Cor vein blood from cor sinus or great cardiac vein	15.1	12.7	2.6	10.1	8.3	41.6	50.2	0.85	9.2	8.6	123.0	119.0		
		20.7	20.2	5.0	15.2	15.3	42.2	52.8	0.70	6.3	5.4	155.0	152.0		
		20.3	14.8	4.6	10.2		42.7	51.4	0.85	8.4	6.1	96.2	94.5		
		15.5	12.5	3.6	8.9	7.8	34.4	40.7	0.66	18.8	16.9	213.0	218.0		
		19.8	18.8	6.2	12.6	13.1	33.9	43.9	0.79	23.0	19.3	137.0	141.0		
		24.8	21.3	6.4	14.9		40.7	49.0	0.83	24.2	18.0	89.0	90.0		
		18.1	17.6	9.8	7.8	13.3	51.3	57.8	0.80	33.0	22.7	135.0	135.0		
		22.8	17.2	3.3	13.9		28.1	39.7	0.71	65.6	52.7	167.0	181.0		
Goodale et al [4]	Anesthetized dog Cor vein blood from cor sinus									15.3	9.0	79.3	75.3	1.99	1.07
			17.2	4.1	13.1		31.8	44.5	1.0	12.2	6.9			1.91	0.95
Bing et al [5]	Normal human Cor vein blood from cor sinus		16.5	5.0	11.5	13.2									
Gregg et al	Anesthetized open-chest dog Cor vein blood from anterior cardiac veins		15.8	4.9	10.9										
			17.8	7.9	9.9										

ventricle (coronary flow times oxygen arteriovenous difference) approximates 19.5 cc./min./100 gm. of left ventricle. In the anesthetized dog the values generally range from 8 to 10 cc./100 gm. left ventricle/min. A range similar to that in the anesthetized dog is indicated for the normal human using the nitrous oxide method for determination of coronary flow. In the heart-lung preparation the oxygen consumption is generally considerably less, approximating 4 to 6 cc. oxygen/100 gm./min.

No data are available for the metabolism of the right heart per unit of myocardium. This is so because it is technically impossible to cannulate the main anterior cardiac veins draining the right ventricle, and as yet there are no data to show that all the anterior cardiac veins have the same oxygen content so that any one of them can serve as the source of venous blood.

The values for cardiac output and work appear to be considerably less in the normal human as compared with those in the unanesthetized dog. However, as to be expected, the values in the dog progressively decrease as the animal is anesthetized, chest opened and heart and lungs isolated, the latter values for cardiac output being as low as 400 cc. per minute and for cardiac work 0.45 kgm. per minute per 100 grams left ventricle. It is obvious that values in the latter preparation are too far removed from normal to warrant intensive consideration. For the right ventricle, many separate determinations of right coronary inflow and metabolism exist, but none have been made with associated measurements of cardiac output, pulmonary artery pressure and work. In Table 10 are included measurements of the latter in the normal human in which the cardiac output and work have been calculated per 100 grams of right ventricle per minute. Such values approximate 8000 cc. and 1.4 kgm. These are much less than those values obtained in the same heart for the left ventricle. While such a derivation is unsatisfactory, the range may serve as a rough index of the level of cardiac output and work per unit of weight of the respective ventricle. Whether these levels for coronary flow, cardiac metabolism, output and work will prevail when less noxious methods can be employed is unknown.

The level of cardiac metabolism and work of the heart is a figure of fluctuating magnitude and can be altered by many dynamic situations. The problem is particularly complex because the heart has a sizeable metabolism even when it is not beating. When the heart is made to fibrillate, its metabolism is reported to exceed that of the heart before fibrillation, i.e., the heart doing no external work may have a higher metabolism than the heart doing known amounts

coronary sinus, the oxygen saturation varies from 12 to 53 per cent, with an average of 23 per cent, which is much lower than that obtained in mixed venous blood (approximately 70 per cent saturation) In the right heart, the right coronary artery-anterior cardiac vein oxygen difference of 9 0 to 13 57 volumes per cent is of the same order of magnitude as that in the left coronary artery [68]

When the heart is separated from the rest of the body (heart lung or isolated heart), the coronary oxygen arteriovenous difference is much lower, approximating 4 7 volumes per cent with extremes from 1 5 to 10 volumes per cent, the larger extractions occurring late in such experiments [4,37,38,91]

Such a degree of oxygen extraction greatly exceeds that found in other body regions In the liver, the extraction is from 2 5 to 4 5 volumes per cent in the normal human by portal vein catheterization [10] in the kidney 2 to 4 volumes per cent in normal humans by renal vein catheterization [77,95] in the extremities 3 3 to 7 3 volumes per cent in normal humans or anesthetized dogs [44,77,9] in the cerebrum of humans, 1 5 to 8 5 volumes per cent by catheter in the internal jugular vein [35,67,68] The extraction values for the heart even exceed those for exercising skeletal muscle [53]

This very large extraction of available oxygen by the normal heart indicates that any significant increase in oxygen need by the heart must be met by an increase in coronary blood flow, which could be effected either by the opening of additional capillaries or by an increase in volume flow in those capillaries already open This separates the heart from all other organs

The very high oxygen extraction from the myocardial capillaries as compared with other vascular beds could result from a relatively low blood velocity, high metabolism, or high level of vascularity, the latter two of which are known to be high as compared with other tissues [15,97]

Similarly, the carbon dioxide content of coronary venous blood greatly exceeds that found in mixed venous blood samples simultaneously withdrawn The respiratory quotient for the left ventricle falls within a normal range of 0 66 to 0 85 (Table 9)

Cardiac Work and Metabolism. – Simultaneous determinations of cardiac output work, and metabolism have been made in the heart-lung preparation and, more recently with the heart beating *in situ* in the anesthetized and unanesthetized dog and in the normal human subject The data in Table 10 has been compiled from investigations in which the metabolism coronary flow, cardiac output and work are expressed in terms of a common denominator *i e* per 100 grams of ventricle In the unanesthetized dog the oxygen usage of the left

so close a relationship to the oxygen usage of the heart These results in general are substantiated [39, 52, 55, 59, 63]

These experiments indicate that the energy available for the heart beat depends chiefly on the diastolic volume of the heart or the length of its fibers Within certain limits the cardiac work also follows the diastolic size or length of its fibers Ultimately however with a considerable increase in the work the relationship of work to diastolic size decreases until finally the work may actually decrease in the presence of a rising diastolic size However there are no adequate means of analyzing the complex dynamics involved in various modes of alteration of work The linear relation between diastolic heart volume and work or oxygen usage is entirely empirical and the relationship may or may not exist when measurements are made with the heart *in situ* under natural conditions

When the heart rate is altered reflexly via the vagus by raising the arterial pressure within the head [89] or directly by driving it electrically [52] or by warming or cooling the sino-auricular node [53] the heart uses less oxygen in a unit of time but more oxygen per beat at the slower heart rates This occurs irrespective of the diastolic heart volume In heart electrically driven the oxygen usage of the heart is a function of the myocardial temperature

Since the myocardium is constantly perfused by blood containing body hormones electrolytes and food stuffs it is of interest to determine their effect on cardiac metabolism Invariably in such observations the substance must be administered in concentrations much greater than exist normally in the blood stream Observations are largely in the isolated heart or heart lung preparation

Epinephrine in physiological doses is a powerful stimulant to myocardial contraction and greatly increases cardiac metabolism presumably as the net result of its direct effect on the myocardium and of the early increase in heart rate both of which increase oxygen utilization and the decrease in diastolic volume and the subsequent slowing of the heart rate (reflex vagal stimulation) both of which decrease the oxygen usage of the heart [1, 39, 42, 50, 54] Feeding of thyroxin and thyroid gland increases the oxygen usage of the heart [13, 67] *Angiotonin* greatly increases the metabolism and work of the isolated heart and heart lung preparation [61, 72] Insulin has no effect on gross cardiac metabolism but operates only to alter the type of metabolism from carbohydrate to fat [14] Various nucleic acid derivatives enhance myocardial activity in the rabbit and cat heart [19, 33] There is no evidence concerning the effect on cardiac metabolism of the naturally occurring fats carbohydrates or their

of work.[64] *When the mammalian heart is arrested (in diastole without fibrillation) by potassium injection, its metabolism is lowered by as much as 50 per cent.*[83] However, in the latter instance the metabolism is still well above the low level that is characteristic of resting striated or skeletal muscle.

In addition, the possibility exists of the creation of an oxygen debt by the heart. Following a reasonable increase in activity of skeletal muscle, the metabolism (oxygen consumption) remains high *for some time after return of the muscle to a control level of activity.* To study this phenomenon in either ventricle of the heart, simultaneous measurements must be made of cardiac output, aortic blood pressures, the oxygen A-V differences, and coronary inflow for the *respective ventricle before, during, and after augmentation of ventricular work.* Such studies are not available.

The physiological variables which affect cardiac metabolism and work presumably include the diastolic size and length of cardiac fibers, *type of contraction, cardiac nerves, heart rate, temperature,* cardiac output and input, products of its own muscular activity, drugs, hormones, foodstuffs, and electrolytes. Except for the effect of drugs, hormones, load and heart nerves, studies have been largely limited to the heart-lung preparation and the isolated heart.

As already indicated in Chapter 4, a considerable increase in cardiac metabolism and work occurs with the heart beating *in situ* when the arterial load of the right and/or left ventricle is increased by aortic or pulmonary artery constriction or increased venous return,[48] or following stimulation of the cardiac nerve outflow from the stellate ganglia.[3,47,87] This confirms experiments with the heart-lung preparation.[1,5,7,36,37,38] The maximum response of the heart under normal conditions has never been determined. However, the largest responses might be expected with epinephrine or cardiac nerve stimulation.

It would be expected that the oxygen usage would depend in some way on the dynamic adaptation of the heart to its work. The presence of some such correlation was first illustrated by Evans and Matsuoka,[27] who showed that as the diastolic volume of the heart increased, the heart metabolism also became greater. Starling and Visscher[89] showed (1) that the oxygen consumption in the isolated heart under constant chemical and temperature conditions is always the same in any one experiment at a given diastolic volume whatever the amount of work that the heart is performing at this volume; (2) the relation between diastolic ventricular volume and oxygen usage is, within limits, a linear one irrespective of whether the arterial or venous cardiac load is altered, and no other mechanical factor bears

dilation of the heart and reduction in efficiency Efficiencies in a similar range are reported for hearts of normal humans in which the cardiac metabolism was measured by the nitrous oxide method and cardiac output by the Fick procedure[3]

Graphs compiled from the work of Eckenhoff *et al*[60] and indicating the effect of primary changes in resistance cardiac output and oxygen tension are illustrated in figure 58 In this the cardiac output was determined in anesthetized dogs by the Fick procedure and coronary flow by the bubble flow meter A primary increase in cardiac output by gelatine or heparinized blood infusion or a primary elevation of aortic blood pressure by an aortic clamp both augment efficiency as the net result of an increase in cardiac output aortic blood pressure work and cardiac metabolism if the aortic constriction is severe enough so that cardiac output is decreased and if it is not maintained by other means the efficiency decreases A primary decrease in arterial oxygen content depresses the average efficiency greatly largely through a decrease in cardiac output and in the presence of an essentially constant systemic blood pressure and oxygen consumption

These trends in cardiac efficiency in the anesthetized dog following alterations in cardiac output and aortic blood pressure confirm earlier observations in the isolated heart and non innervated and innervated heart lung preparation[27,34,5,66,69] In the latter preparation epinephrine injection and stimulation of the stellate ganglion[27] generally decrease cardiac efficiency through a combination of an increase decrease or no change in cardiac output and an increased blood pressure and increased oxygen utilization Vagal stimulation either directly or reflexly induced in the innervated heart lung preparation increases efficiency as the net result of a lowered cardiac output blood pressure work and metabolism of the heart[27]

By definition mechanical efficiency indicates work done per unit of energy output The work of the heart is performed during the latter part of the period of systole but as in skeletal muscle energy is released by the heart (oxygen used) when it is doing no work Presumably oxygen is used before *during* and *after* ventricular systole A certain amount of oxygen can be used during the early part of systole from the onset of elevation of intraventricular pressure to the time of opening of the pulmonary and aortic valves (isometric contraction period) during which time no blood is moved and no external mechanical work is done Also during diastole oxygen can be used but the muscle fibers are not shortening This may be in part considered as an oxygen debt of the heart due to the

derivatives, of the blood electrolytes (except potassium), or of compounds that occur within the myocardium

Efficiency.—Studies have been made on human subjects and on unanesthetized and anesthetized dogs Some of the data have been compiled in Table 10 In the unanesthetized dog the efficiency approximated 31 per cent [85] In the anesthetized dog with a good cardiac output and blood pressure, the efficiency was found to vary from 7 to 34 per cent (Table 10) In the heart lung preparation, the values are somewhat less The highest efficiencies are generally associated with large outputs together with a high arterial pressure However, if the work is pushed beyond certain limits the oxygen usage may increase at a disproportionately rapid rate with resultant

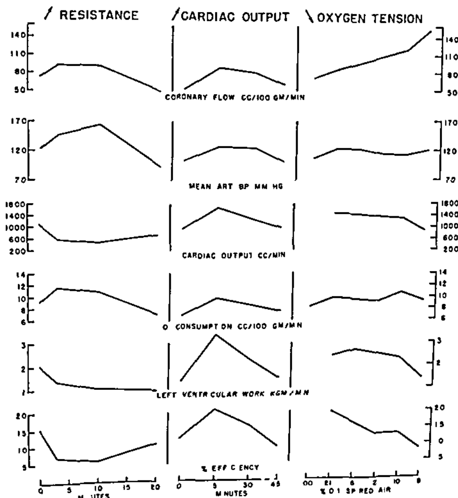


FIG 58.—Effects of primary changes in peripheral resistance cardiac output, and oxygen tension on the heart and coronary circulation in the anesthetized, open chest dog Slightly modified from Eckenhoff *et al* [27]

and glucose utilization by the heart is estimated to account for only 2, to 60 per cent of total cardiac oxygen utilization assuming eventual complete oxidation of these substances to carbon dioxide and water [41 73 93 94]

Certain additional information is available concerning the carbohydrate metabolism in the isolated heart or heart-oxygenator system Gluco e extraction and utilization is increased when the blood lactic acid is decreased or when cardiac work is increased by mechanical means or by epinephrine [8] Similarly lactate usage by such hearts is a function of its blood level the oxygen supply and cardiac work and is inversely related to the blood sugar level [8] Added sodium pyruvate is readily u ed but its utilization is not increased by epinephrine and its addition does not affect cardiac glycogen blood sugar or lactic acid levels [11] It must therefore affect either non-carbohydrate usage *i e* fat or protein or it may alter (increase) oxygen usage without affecting any other oxidation The glycogen content which is constant for hours with moderate work (heart lung) and largely exhausted with heavy work and with the addition of thyroxin or epinephrine is largely restored by glucose administration and is increased by elevation of the blood ketones [70] but lactate supplement is without avail [7 71 94] Apparently carbon dioxide can be incorporated into the glycogen of the heart which indicates that cardiac glycogen is constantly being broken down and remade [75] Whether any or all of these observations apply to the normal heart remains to be determined

The role of these compounds in cardiac metabolism is not clear However it is believed that lactic acid is the keystone if in abundance it i oxidized and arises directly from the blood if low or lacking in the coronary arterial blood it is obtained from glycogen breakdown In the latter case glycogen is replaced from the blood sugar if the latter is insufficient the glycogen content falls and the heart fails The role of pyruvic acid is not known

There would appear to be a fundamental difference between skeletal and cardiac muscle in their respective usage of lactic acid and glucose Cardiac muscle oxidizes (consumes) large amounts of lactic acid and forms glycogen from glucose while skeletal muscle mainly forms glycogen from lactic acid and oxidizes glucose

Although the total oxygen usage of the heart cannot be accounted for on the ba is of carbohydrate di appearance the proof of the utilization of other substances such as fat in cardiac metabolism leaves much to be desired All evidence i from the heart lung preparation and is along the lines that (1) fat concentrations are less in hearts which have been worked for a time [17 96] although the latter

preceding systole or as a "maintenance metabolism." Evidence for the latter is contained in the observation that when the mammalian heart is arrested in diastole (without fibrillation) by potassium injection its metabolism may be lowered by as much as 50 per cent. However, in the latter instance, the metabolism is probably still well above the level that is characteristic of resting skeletal muscle. In skeletal muscle or the body as a whole the non-contraction oxygen requirements which are not related to work done can be separately quantitated by temporarily stopping the work so that only oxygen usage related to work is considered. However, methods or procedures are not available by which the normal contraction in the heart *in situ* can be temporarily stopped and the resting or maintenance oxygen usage separated. In addition, studies of the extent of oxygen debt of the heart beating *in situ* are not available.

The cardiac efficiency will, therefore, vary in part with the extent of contribution of the resting and isometric contraction period oxygen and post work period oxygen to the total oxygen usage. In general, the former will tend to lower the calculated efficiency at low levels of work and to increase efficiency as the work is increased.

Substance Utilized and Type of Metabolism.—The heart is a machine which converts potential chemical energy into useful work with varying degrees of efficiency. The warm blooded heart is incapable of working more than, at most, a few minutes in the absence of oxygen because the store of substances yielding energy under anaerobic conditions is very limited. Therefore over any prolonged period of time the energy for cardiac contraction must come from the oxidation of combustible materials. The use of these compounds has been intensively studied.

The biochemical characteristics of coronary venous blood clearly distinguish it from mixed venous blood and indicate the substances used by the heart (Table 9). The large extraction of oxygen has already been indicated. The consistently large coronary arterio venous differences of lactate and pyruvate[40,41,6,79] considering the relatively high rate of coronary blood flow, indicate an extremely high rate of myocardial utilization of these metabolites in the open-chest or normal intact, lightly anesthetized dog. In the same type of preparation, glucose is removed by the heart in relatively small amounts and often not at all,[41] especially at the higher lactate levels. These findings, in general, confirm those obtained when the heart is in a more abnormal state, *i.e.*, the heart lung preparation (in which an artificial oxygenator is substituted for the lungs to obviate the removal of sugar by the latter organ and its subsequent transformation into lactic acid).[9,31,37] The combined lactic acid pyruvic acid

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workers feel that the attendant cardiac edema may be a factor, (2) short chain fatty acids, such as beta hydroxy butyric acid when added, can be utilized by the heart up to 80 per cent of its total metabolism, [96] (3) the R Q is 0 70 when sugar is essentially absent from the circulating blood [17] However, there is no evidence that long chain fatty acids can be burned by the heart, and no changes have been observed in the fatty acid content of the perfusing blood

The possibility that nitrogenous compounds can supply energy for oxidation has also been investigated Evidence indicates that in the aglycemic heart-lung preparation, no significant increase occurs in the ammonia, urea or NPN in the venous blood [17] and in the aglycemic, isolated beating cat heart, the addition of glycine label led with heavy carbon in the carboxyl position does not increase the respiratory carbon dioxide [74] However experiments with acetate similarly prepared indicate a usage of 20 to 30 per cent [76]

The chemical substance initially exploded during myocardial excitation, and which releases the energy for the sequence of events leading to systole or contraction of the ventricles is as yet unknown

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and/or the myocardial arteries they may involve one or all vessel coats and may occur with or without infarcts Among these lesions necrotizing arteritis a prominent feature of malignant hypertension and occurring also in most of the other clinical states indicated is of particular interest for it has been produced experimentally by renal ischemia in the dog [4] by sensitization of rabbits through the injection of horse serum [14] and by unilateral nephrectomy in rats combined with injections of desoxycorticosterone [134] The essential morphologic change in the arterial wall is a fibrinoid necrosis of the media More recently interest in these lesions has been enhanced by the discovery that multiple injections of the strong base allylamine a derivative of tissue breakdown and possibly coming from the kidney lead to a chronic form of necrotizing arteritis restricted to the coronary arteries (and some mesenteric vessels) and, in which there is progressive necrosis of the media with intimal and medial hemorrhage and thickening of the media and intima so that in six to eight weeks an obliterative endarteritis is produced [119] The lesions are not related to diet can be produced in the dog but not in the cat or rat and do not alter blood pressure Lesions identical morphologically with those induced by allylamine but distributed throughout almost all arteries and arterioles have been produced in dogs by feeding a high fat diet for two months or longer and then experimentally inducing renal insufficiency in any one of several ways The lesions can be prevented or retarded by vitamin E by cholesterol or by omitting fat supplement for four weeks or longer [89] Further experimentation is necessary to determine what role if any these lesions normally play in the etiology and pathology of vascular disease in man or in experimental animals

Atheromatous Lesions —The most important lesion of the coronary artery is the atheroma It occurs at all ages from birth to old age but is more frequent in the latter half of life Human necropsy studies indicate that between fifteen to twenty five years of age 10 to 11 per cent of the coronary arteries are sclerotic from twenty five to thirty years of age 23 per cent from thirty to thirty five years of age 27 per cent from thirty five to forty 34 per cent from forty to forty five 32 per cent and from forty five to fifty 50 per cent [14] Serious obstruction of a coronary artery rarely occurs except in a previously sclerotic vessel This obstruction may arise from the atheromatous process itself or from a thrombus or intramural hemorrhage which is associated with the atheromatous lesion The atheromatous process with its associated sequelae accounts for most of the serious obstructions of the coronary arteries In a typical study of 6800 consecutive autopsies thrombosis on an

Chapter 8

THE CORONARY CIRCULATION IN HEART DISEASE AND HEART FAILURE

THE conditions of the heart which may lead to heart failure are well known. The heart with coronary artery disease, with an increased load from valvular disease or augmented blood pressure, or with primary involvement of the myocardium may fail early or ultimately in a hypodynamic state or from ventricular fibrillation or it may never fail. Within recent years, considerable information has become available concerning the mechanisms involved in heart disease. It is mainly the attempts to elucidate the physiological effects of coronary artery disease with which we are concerned.

HUMAN CORONARY ARTERY LESIONS

There are various non-atheromatous and atheromatous lesions which affect the coronary arteries. Only those lesions which reduce or occlude the lumen of the coronary artery and thus alter coronary blood flow are important.

Non Atheromatous Lesions.—These lesions, recently reviewed,[136] constitute at most 5 to 10 per cent of all coronary lesions and include congenital anomalies, medial calcification, inflammatory lesions, aneurysm, embolism and neoplasm. Of these only aneurysm is presumably without effect on coronary flow.

The congenital anomalies include marked hypoplasia of both coronary arteries, absence or reduplication of a main coronary artery, presence of accessory coronary orifices, or one or both coronary arteries can arise from the pulmonary artery. Except in the last instance, there is usually a sufficient collateral circulation so that the heart functions normally and without symptoms. In children, the larger coronary arteries may be partially or completely occluded by medial calcification with fibroblastic proliferation of the intima. The cause is unknown.

Inflammatory lesions with obstruction or obliteration of the coronary lumen can occur in many diseases such as subacute bacterial endocarditis, syphilis, tuberculosis, brucellosis, rheumatic fever, polyarteritis nodosa, typhus, lupus disseminata, thrombo-angiitis obliterans, serum sickness, malignant hypertension and typhoid fever. The lesions may involve the coronary orifices, the epicardial

wall is nourished from two sources the adventitia and the lumen of the vessel In the coronary arteries there are small arterial vessels penetrating the adventitia and most of the media which anastomose with the vasa arising from the arterial lumen The vasa arising from the adventitia are much more abundant than those arising from the lumen of the coronary artery Presumably the small arterial vessels in the adventitia and media and the intimal nutrient vessel ultimately drain by small veins into the adventitia Figure 59 illustrates a typical mode of origin and pattern of intimal vasa vasorum in a presumably normal coronary artery

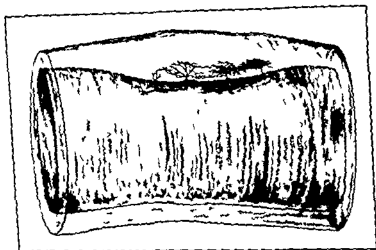


FIG 59 —Coronary artery injected and cleared with adventitia removed Vasa vasorum arising from intima and forming tree like pattern (Winternitz et al [8] courtesy of Charles C Thomas)

The morphological changes in the coronary arteries of man with atherosclerosis have been described many times but difference of opinion exists as to the sequence of events in the lesions and as to what is the initial lesion The earliest stage of coronary atherosclerosis may begin in infancy as a yellow streak in the intima of the involved vessel progressing and extending during childhood and adolescence These early atherosclerotic plaques occur in 2 per cent of infants under six months and in a very high percentage of children over eight years [2,63] The fact that at any age the intima of the coronary epicardial arteries is so thick relative to that of other arteries of comparable size is believed by some to establish the basis for the predilection of atherosclerosis for this artery [20]

Macroscopically the involved arteries may show nothing or may

arteriosclerotic basis (43 per cent), arteriosclerosis with or without infarction (41 per cent) and intramural hemorrhage (8 per cent) presumably on an arteriosclerotic basis made up 92 per cent of the series with the remaining 8 per cent divided between embolism, inflammation and syphilis [1,8]

In the coronary vessels these obstructing lesions arising from an atheromatous process are restricted to the arterial side and almost invariably, to the main stems of the coronary arteries or to their immediate large branches *i e* the epicardial arteries Over 50 per cent of the occlusions may be found within 3 cm and about 80 per cent within 6 cm of the coronary ostia [70,150] Although there is considerable variation in the distribution of lesions between the coronary arteries, the left anterior descendens is generally most often involved with about 66 per cent of all occlusions being in this artery,[150,193] and about 50 per cent of all occlusions occurring in its proximal third

With old age and senescence the vessel structure in the epicardial and myocardial arteries (but not in the myocardial twigs) is markedly altered in the absence of arteriosclerosis [5,196] In the epicardial arteries the intima at birth made up of a layer of endothelial cells covered by a single internal elastic lamella changes and thickens so that it ultimately becomes several times the thickness of the media and encroaches on it The intima of the coronary arteries lying in the epicardium is believed to be much thicker in males than in females even in newborn infants and in both instances much thicker than that of any artery of similar caliber elsewhere in the body [30] The media initially made up of circular smooth muscle and elastic fibers and the adventitia a meshwork of connective tissue containing elastic fibers both lose their elastic fibers with age These changes are most rapid in the left anterior descendens artery and slowest in the right coronary artery The myocardial arteries undergo fibro elastic changes in the intima and media and atrophy of the smooth muscle in the media and develop irregular patches of connective tissue

The arteries and veins are metabolically active structures consisting of muscle cells fibroblasts and elastic and collagen fibers and an intercellular material through which nutrition is brought to and waste products removed from the vessel The mode of nutrition of a normal vessel wall is poorly understood but the presence of small nutrient vessels or vasa vasorum in the walls of arteries and veins has been known for many years These vasa do not exceed 10 microns in diameter and are quite frequent in the walls of veins but are not numerous in the walls of normal arteries [1,3,139,151,15,195] The arterial

liquefaction by macrophages with minimal connective tissue reaction and support is dominant [illegible]

Thrombosis and Mechanism of Closure —Stenosis or occlusion of a coronary artery may arise from a number of events associated with the arteriosclerotic process Fragments of arteriosclerotic plaques in the coronary artery on rare occasions break off and are carried further down the artery there to lodge and occlude the lumen [9] The plaques themselves may become so large as also to occlude the lumen Thrombosis if present almost invariably occurs in association with atherosclerosis of the artery usually at the point of stenosis by means of an arteriosclerotic plaque and



FIG 61 Recent thrombosis of the anterior descendens ramus of the left coronary artery The artery is the seat of advanced sclerosis and the thrombus has formed on a ruptured atheromatous plaque (Wartman [118])

generally at the point where the intima is roughened or broken thus possibly allowing the liberation of substances which hasten coagulation Figure 61 illustrates a typical thrombus formation in the region of an atheromatous plaque

It has been convincingly demonstrated [illegible] that in the presence of sclerotic lesions of the coronary arteries the atherosclerotic plaques in the intima become richly vascularized by capillaries derived from

be thick tortuous and hard There may be only fatty streaks in the intima or raised and irregularly shaped yellowish plaques may be seen in the intima, often bulging into the lumen The intima may be annularly or eccentrically greatly thickened by atheromatous material and fibrosis and the lumen reduced in diameter or occluded The drawing in figure 60 illustrates the rich vascularization of the intima and media which develops in a coronary artery in association with the appearance of an intimal lesion

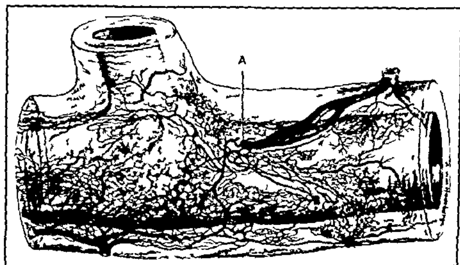


Fig 60 —Coronary artery injected and cleared with adventitia removed Remarkably extensive and bizarre pattern of vasa vasorum A large sinus presumably venous is seen at A (Winternitz *et al*[19] courtesy of Charles C Thomas)

The microscopic changes are largely restricted to the intima Various changes can be observed There may be only droplets of fatty material within the intima slightly raising the surface and surrounded by fibroblasts There may be intimal thickening by connective tissue large intimal plaques with areas of degeneration and necrosis containing soft atheromatous material and macrophages with lipoids intimal hemorrhage and a new capillary circulation directly connected to the coronary arterial lumen and adventitia fraying or destruction of the elastic lamellae intimal ulceration and hemorrhage thrombus formation calcification and hyalinization With the larger plaques the media may be atrophic and displaced to the periphery by fibrosis There is some evidence that the dominant change in younger persons is a fibroblastic proliferation of the intima leading to narrowing of the lumen while in the older age group, the deposition of lipids in the intima and their ingestion and

probable cause of the condition Consideration of some of the associated circumstances already alluded to that the lesions contain fatty materials that the disease is more frequent in males in diabetics on the occasion of increased blood cholesterol (hereditary xanthomatosis) in overweight individuals in hypertensives that the lesions are largely restricted to epicardial arteries the aorta renal and cerebral vessels suggests that many factors such as hormones diet blood lipids and mechanical factors (strain) may be involved This has laid the groundwork for theory and experimental investigation It has been suggested that (1) the lipid deposit and lesions arise from a non selective infiltration from the plasma in the presence of a primary lipemia or hypercholesteremia [158] (2) the primary factor is an invasion of the subendothelial layer of the intima by foam cells produced in and arising from the liver as a result of an increase in blood content of cholesterol [85] (3) the primary factor is the *cumulative* effect of many fatty meals in producing transient plasma showers of large lipid particles which enter the vasa from the lumen of the coronary artery and are blocked in the intima [116] (4) *local* metabolic derangements[170] cause a local overproduction of lipid (5) the primary lesion is a loosening of the connective tissue ground substance in the intima in those vessels under *greatest* mechanical strain with the lipid content of the plasma secondarily determining the degree of fatty *infiltration* [4] (6) the initial stage is an injury to the arterial wall which localizes the lesion The injury may arise as the result of the formation of a film or precipitate over the intima thus interfering with the nutrition and oxygenation of the vessel wall [23 80 123] (7) the initial stage arises from frequent small subintimal hemorrhages which result from the increased vascularity of the intima with age [195]

These theories or hypotheses are poor substitutes for facts and are included only for the sake of completeness

Attempts have been made to study these lesions in species in which they occur spontaneously and to induce such lesions in experimental animals in which they do not occur naturally

Arterial intimal sclerotic lesions (also aortic lesions) occur spontaneously and with considerable frequency in birds [19 43] In distribution and morphology these lesions closely parallel those seen in man Dauber was unable to demonstrate spontaneous coronary artery intimal lesions in young chickens However about 70 per cent of cockerels less than one year old were shown to have coronary intimal lesions [138] In this instance the primary lesion is believed to be a medial degeneration which antedated the proliferation of intimal tissue These naturally occurring coronary artery lesions are not

the intima and the adventitia. Such an increase in vascularization can be innocuous. However, the soft, easily compressible material of the atheroma offers no support against the capillary blood pressure and hence a small, intramural capillary can easily rupture with formation of a hematoma (Fig. 62). This intramural hemorrhage can also be small and of no trouble, or the coronary artery can be occluded by massive hemorrhage into the wall by such capillary rupture with the formation of a large hematoma which pushes the intima centrally and blocks the lumen by virtue of its size or by rupture through the intima and subsequent thrombus formation.



FIG. 62.—Massive recent hemorrhage into the wall of the anterior descending ramus of the left coronary artery. The lumen (c) is occluded because of compression by the intramural hemorrhage (a). The endothelial lining (b) is intact and there is no thrombus. (Wartman[18])

Necropsy records indicate that approximately 50 per cent of such intimal hemorrhages lead to thrombus formation at the site, and that hypertensives with coronary sclerotic lesions are 2 to 3 times more liable to have intimal hemorrhages than normotensives with similar extensive sclerotic lesions.[131] It is thus a very important cause of coronary constriction and insufficiency.

EXPERIMENTAL ARTERY LESIONS

Coronary Atheromatous Lesions.—Nothing during life or after death of persons with coronary atherosclerosis stands out as the most

clusion in myxedema, diabetics with high blood lipid and cholesterol values, and the high incidence of such lesions in systemic xanthomatosis associated with increased blood cholesterol and lipids has focused attention on the idea that alterations in lipid ingestion, absorption, metabolism or excretion may favor or be necessary for the disease. However, the evidence is not impressive that lipid changes so obvious in diabetes, xanthoma, and nephrosis are also present in most cases of coronary atherosclerosis.

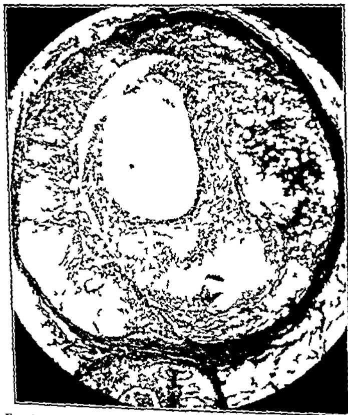


Fig 63.—Arteriosclerosis of the coronary artery in the dog showing many of the sequelae of human arteriosclerosis. The lumen is narrowed by diffuse atheromatous deposits. Within the plaques are hemorrhage, hyalinization and calcium. The media has been partially replaced by lipid deposits. Hematoxylin and eosin stain × 86. (Steiner et al [165])

To arrive at significant conclusions, the normal physiological variations in blood lipid values must be defined for males and females in the various age groups. Blood cholesterol values in different normal individuals within the same age group fluctuate within wide

associated with elevation of any lipid fraction of the blood, and the feeding of cholesterol with associated increase in blood cholesterol levels does not increase the number of lesions but accelerates the arteriosclerotic process especially in the intima causing lipid material to be laid down at the points of pre-existing spontaneous lesions and resulting in the formation of stenosing plaques of the atherosclerotic type[133] In the rat rabbit dog, monkey cat, guinea pig, and hamster, spontaneous coronary artery intimal lesions are rarely found

Coronary lesions have been produced experimentally in the rabbit, chicken, and dog [21, 31, 1, 167, 168] It has not been determined to what extent coronary lesions can be induced in other species Coronary lesions are produced in the rabbit and chicken by adding cholesterol to the diet and in the dog by the addition of cholesterol combined with thiouracil Large amounts of cholesterol (up to 10 grams daily) fed to the rabbit and chicken produce the lesions only after several months of feeding this is accompanied by a 3 to 10-fold augmentation of the normal serum cholesterol values (60 to 120 mgm per cent) In the dog after a 10-fold increase in blood cholesterol over normal (100 mgm per cent) for four months, the lesions appear, although maintenance of blood cholesterol values at about 400 mgm per cent for twelve months is also effective[168] In all instances the increase in blood cholesterol is associated with a concurrent increase in other blood lipid fractions and the lesions are preceded by extensive cholesterol deposits in many organs and tissues

Intravenous and intraperitoneal injections into the rabbit dog and monkey of various macromolecular substances such as polyvinyl alcohol pectin gum acacia gelatin cellulose also cause atheromatous lesions of the coronary arteries morphologically resembling the lesions in man except that the lesions contain the injected substance rather than cholesterol or lipid [6, 9]

The naturally occurring or experimentally induced coronary lesions are similar in many respects to the human lesions with narrowing of the lumen plaque formation marked intimal thickening through accumulation of foam cells containing fatty material connective tissue proliferation and compression of the media with degeneration of its muscle cells but the endothelium remains intact and no ulceration or thrombus formation has been observed Figure 63 illustrates such a lesion in a coronary artery of the dog following long continued feeding of cholesterol and thiouracil[168]

The experimental production of coronary intimal lesions by cholesterol feeding or by macromolecular substances together with the clinical evidence of the high incidence of coronary stenosis and oc-

electrical and chemical cauterization freezing vitamin C deficiency injection with irritating substances such as acids silica injection of bacteria and their toxins lead nicotine horse serum digitalis caffeine mercuric chloride uranium nitrate tyramine viosterol epinephrine thyroxin (See reviews by Katz [84] and Duff [32]) and by stimulation of cardiac nerves [54]

Means to prevent the spontaneously occurring or the cholesterol induced lesions in the extracoronary vessels have centered around the diet and the hormones In the chicken spontaneous aortic lesions are not prevented by dietary fat restriction [73] but are reduced by the administration of desiccated thyroid and potassium iodide [74] Lipotropic substances methionine lipocaic choline betaine and lecithin reduce the lipid concentrations in tissues but their possible protective effect on the aortic lesions of the cholesterol fed rabbit or diabetic dog is debatable [131, 56, 166, 171] It is a curious fact that *alloxan* diabetes protects against cholesterol induced atheromas [31] whereas diabetes induced by pancreatectomy may lead to marked atherosclerosis [31] In the aorta of rabbits cholesterol induced lesions are retarded or prevented by the administration of thyroid gland and potassium iodide [173] by an organic iodide [15] and by testosterone and estradiole in female rabbits with intact gonads but not in male rabbits [14, 107] Each agent which is effective against atherosclerosis also prevents hypercholesterolemia except the organic iodide which prevents lesions in the presence of a marked hypercholesterolemia

From the preceding the conditions of the experimental lesions differ in some respects from the human lesions there must be large amounts of cholesterol in the diet and the hypercholesterolemia must be marked the deposit observed in the coronary arteries is part of a general systemic infiltration of lipids in the tissues the hypercholesterolemia always precedes the deposition of cholesterol but no definite relationship has been established between the height and duration of hypercholesterolemia and the degree of arteriosclerosis there is no ulceration of the intima or thrombosis of the artery

If cholesterol induced atherosclerosis is the duplication of Nature's experiment in man then future studies using it would profit by the establishment of adequate criteria for the production of the experimental disease and evaluation of means for its prevention or retardation To date *most* experiments have been done without sufficient regard for the control of age weight sex and diet Unfortunately most experimental studies of atherosclerosis have been made on the aorta and very few on the coronary arteries Since

limits the cholesterol in the blood of a normal adult individual is essentially constant during the day and at least for a few years and is not altered significantly by environmental conditions, living habits, state of nutrition moderate over-feeding with cholesterol with or without fat, although the level can be significantly increased by daily feeding of 100 grams of egg yolk powder containing 8 grams cholesterol and 14 grams lecithin [1,7,166] It is debatable whether blood cholesterol and lipid values are increased in those individuals of any age with marked coronary artery disease [51,90,97,109,110,165,166] It is possible that *following* coronary occlusion cholesterol values are increased, although if true, it is not known whether these values existed before occlusion or were caused by it [117] The fact that the range of values obtained varies greatly with the method and technical procedures used *does* not inspire *confidence* in the values reported for the cholesterol and lipid contents of the blood

The fact that macromolecular substances can induce coronary lesions raises the possibility that increase in size (without increase in quantity) of naturally occurring substances in the blood stream such as cholesterol-protein compounds, may implement the human *coronary lesion No good evidence exists on this point although* it is reported that following fatty meals showers of large fatty particles appear in the blood stream [116]

No experiments have been reported which prove that experimental coronary artery lesions can be reduced or prevented by any treatment

Extra coronary Atheromatous Lesions —Brief mention is made of these lesions because of their similarity in man to the coronary artery lesions They occur spontaneously only in the aorta of the chicken,[27] but they have been induced in different species and in almost every artery and vein, including the aorta and cerebral vessels in which they occur in man The aortic lesions have been *induced in the chicken by cholesterol feeding* [3] *in the dog by* cholesterol and thiouracil feeding [165] in the rabbit by cholesterol feeding or intravenous injection [17] by a high protein defatted casein diet without cholesterol [110] and possibly by aortic constriction central to the renal arteries [23] In all instances except the last there is an associated marked hyperlipemia

Attempts to produce the lesions in the aorta and peripheral arteries of the dog rabbit guinea pig and rat by mechanical infectious and toxic means have all failed These attempts have led variously to inflammatory lesions medial degeneration necrosis calcification and aneurysm formation but not to intimal atheromas Some of the agents employed include ligation pulling and pinching of arteries

inserted into an adapter fitted to the distal end of the hose A peripheral resistance (PR) was introduced distal to the constricting tube and separated from it by a 10 cm length of large diameter hose (20 mm I D) For the PR mechanism one of a similar set of metal tubes 20 mm long (I D ranging from 0 5 to 3 0 mm) was used Blood or acacia solution with a viscosity approximating that of blood was allowed to flow by gravity at a constant hydrostatic pressure and the outflow from the PR tube was timed and measured

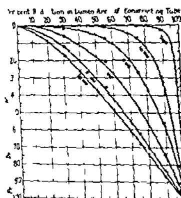


Fig 64

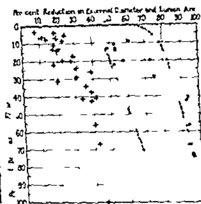


Fig 65

Fig 64 Graph showing variations in flow reduction caused by fixed constricting tubes when different peripheral resistances were imposed distal to the constricting tube Fixed constricting tube diameters 2 5 2 0 1 5 1 0 0 5 mm reference constricting tube diameter 3 mm Opposite each curve is indicated lumen diameter of the corresponding peripheral resistance tube acacia solution (specific viscosity 4 0-4 5) used as fluid medium (Shipley and Gregg)

Fig 65 Percentage reduction in blood flow plotted against per cent decrease in external diameter (+) and lumen area ( ) of intact blood vessels in anesthetized dog The two broken line curves represent the relationship of external diameter (A) and lumen area (B) to per cent reduction in flow as reported by Mann and co-workers (Shipley and Gregg[1])

In figure 64 are plotted percentage reductions in lumen area of the constricting tube versus percentage decreases in flow when different peripheral resistances were imposed distal to the constricting tube The internal diameters of the PR tubes are indicated beside the respective curves In the high PR range (small bore PR tubes) the constricting tubes limit flow very little until the percentage decrease in lumen area is very high Actually when the peripheral resistance is high as much as a 90 per cent reduction in lumen area

atheromatous lesions of the aorta do not add to the work of the heart or lead to heart failure, such weighting of experimental studies is justified only provided that the aortic or peripheral arterial lesions mirror simultaneously occurring and similar lesions in the coronary arteries. Clinically, the correlation between such lesions in these two regions is regarded by some as poor. The necropsy studies of Yater *et al*[193] on 457 men from eighteen to thirty nine years of age suggest that coronary arteriosclerosis is a specific disease of the coronary arteries and not part of a more generalized arteriosclerosis.

As yet then, experimental studies directly attacking the problem of coronary atherosclerosis have not been productive in elucidating the mechanism of or preventing the induced lesions. However, the functional consequence and compensatory physiological responses to controlled experimental coronary constriction and occlusion in acute and chronic animals have been extensively investigated.

THE EFFECT ON CORONARY FLOW OF PARTIAL REDUCTION IN LUMEN OF THE EPICARDIAL ARTERIES

Although this would seem to be a very simple problem in which it could be predicted safely that intrusion on the lumen by an atheromatous plaque or localized thickening of the intima would decrease coronary inflow, this is not necessarily true. The flow may or may not be affected and no definite predictions can be made. According to Poiseuille's law, the rate of flow through small tubes is directly proportional to the 4th power of the radius of the lumen and to the pressure drop across the two ends and is inversely proportional to fluid viscosity and length of tube. If the lumen of a given length of vessel is reduced by a fixed amount and the viscosity is not altered, then the rate of flow through the constriction will be governed by the pressure difference across the two ends of the constricted segment. The factors determining this pressure difference are the pressure on the upstream side of the constriction, the resistance to flow through the constricted segment and the peripheral resistance of the arteries and vascular bed distal to the constriction.

As a first approach, experimental determinations were made in an artificial system in which the above factors could be more easily varied and controlled. The apparatus used consisted of a large reservoir tank to the bottom of which was connected a rubber hose of large diameter (I.D. 2 cm.). A metal tube 10 mm. in length with a cylindrical lumen diameter of 0.5, 1.0, 1.5, 2.0, 2.5 or 3.0 mm. was

external diameter of a vessel progressively decreases (by mechanical or active constriction) it can be shown that the same percentage decrease in the existing external diameter will cause an increasingly greater percentage decrease in the existing lumen area. A second and equally unpredictable factor which may alter the ultimate influence of a localized constriction upon flow is the response of the peripheral bed. When the flow to the bed is reduced by central constriction the peripheral vessels may dilate as a result of the associated ischemia and the flow may tend to increase, the combined result of which will be a new equilibrium.

Hence since the peripheral resistance in any one vascular bed is constantly changing and will be altered (decreased) by the anoxia induced by any central constriction and since the effect on flow of any central reduction of lumen is a function of how much that resistance is in relation to the peripheral resistance, no predictions can be made as to the effect on blood flow when the coronary artery is constricted in the dog by known amounts. In the coronary bed preliminary unpublished observations have indicated that the peripheral resistance is relatively high and generally sizeable reductions in lumen are necessary before inflow decreases. Thus the reduction of the lumen of a coronary vessel may be of little functional importance to the vascular bed supplied by that vessel when the rate of flow is already low but the same constriction may seriously limit flow to the same bed just at the time when the requirements of the latter are greatest and flow would otherwise be much greater.[17]

Obviously this compensatory dilatation of the coronary bed in the presence of constriction of its central artery is limited and flow through it will ultimately fall significantly. The extent to which the flow can be reduced and still maintain systolic shortening in the region fed by the coronary artery has not been determined. However significant changes do not occur in the electrocardiogram until the flow is reduced approximately 70 per cent.[185] These changes are reversible and disappear completely within three to five minutes after release of the occlusion.

THE CARDIAC RESPONSES TO SUDDEN OR GRADUAL COMPLETE CORONARY OCCLUSION

These are the most dramatic episodes in which the coronary system is involved and have been studied extensively experimentally. Of the hearts which develop a coronary occlusion many will fibrillate immediately or within a few days and die. Others will

of the central constricting tube is necessary to induce a readable reduction in flow in the system. With a lesser peripheral resistance (larger bore PR tubes) the central constricting tubes are much more effective in limiting flow, and this effect increases until with a 5 mm. PR tube there is essentially a linear relationship. It is evident therefore, that the peripheral resistance mechanism at the end of the flow circuit plays an extremely important role in determining the extent of flow reduction caused by the more central constriction.

One would anticipate quite similar variations in flow reduction in an *in vivo* preparation where the PR of a given vascular bed may undergo considerable change through vasodilation and constriction. Experiments have been made in anesthetized dogs in which the flow was measured in the carotid artery by a rotameter, and the same artery was constricted by bivalved Lucite blocks, 10 mm. long, with centrally placed cylindrical holes of graduated diameters (0.5 to 5.0 mm.) applied to the vessel peripheral to the rotameter. The mean flow was noted before and immediately after placement around the artery. The external diameter of the artery without constricting block was determined by encircling the vessel 3 times with a fine silk thread, tying the knot snug to the artery, cutting the thread and measuring while still wet its length from which the external diameter was computed. At the end of the experiment and without disturbing the artery length, the external diameter of the vessel was again determined, while a small glass rod of measured diameter was inserted into the arterial lumen through a slit. From this data the cross sectional area of the arterial wall and the vessel lumen were calculated. The combined results of two experiments are presented in figure 65, in which are plotted the percentage reductions in flow versus percentage reduction in external diameter (+) and lumen area ( ) of the artery. Each point indicates the percentage change from the control to the mechanically constricted state of the artery. The blood flow ranged from 140 to 828 cc. per minute under different conditions and mean blood pressure remained constant during the actual determinations. In contrast to the orderly sequence of changes in flow observed with the gravity system in figure 64 the same relationships recorded *in vivo* with successive constrictions are decidedly irregular even though the PR of the bed was not intentionally altered. When nitroglycerine was given or hyperemia induced the points were even more irregular.

It is evident from the wide scattering of points in figure 65 that there exists no fixed relationship between percentage reduction in flow and percentage reduction in the luminal or external dimensions of a vessel *in vivo*. This arises from at least two factors. As the

Locke's solution apparently has a larger metabolism than before fibrillation.

A satisfactory explanation of the mechanism by which ventricular fibrillation is initiated spontaneously after coronary occlusion or after the various effective agents is not available. However, the work of Wiggers[190,191] and King[48] has done much to clarify the situation. When an electric current was applied to the heart, ventricular fibrillation was induced only when the stimulus was strong enough and a portion of it was applied during the last 0.03 to 0.06 seconds of systole (the vulnerable period of the ventricles). If applied at any other moment of the cardiac cycle, a premature ventricular contraction followed, but the electrical stimulus had no fibrillatory effect, no matter how strong. In ventricular fibrillation spontaneously occurring during coronary occlusion the causative stimulus must probably come from within the heart. According to Wiggers' concept, one of the spontaneously occurring stimuli which arise in the heart from ectopic foci after coronary occlusion, and which lead to premature systoles, probably falls within the vulnerable period of a normal heartbeat or that of a premature heartbeat arising from discharge from another center, and fibrillation then follows. The probability that such a naturally occurring stimulus has an adequate intensity is enhanced by the observation that myocardial ischemia greatly reduces the threshold of the ventricle to artificial fibrillation during coronary occlusion.[194] Thus a natural electrical impulse discharged at the proper moment is sufficient to fibrillate the ventricles in the presence of a low fibrillation threshold arising from myocardial ischemia.[55]

Experimentally in dogs it is rarely possible to revive a heart with an occluded coronary artery unless the occlusion is first removed and the ischemic area *flooded* with arterial blood. Even here, it can be shown that the release of the coronary artery and the reentrance of blood into the occluded region will itself often induce fibrillation. However, it is a relatively simple matter to revive ventricles which have fibrillated spontaneously without coronary occlusion or following electrical stimulation. Such procedures have been used in laboratories for many years. Early in such work it was found that the injection of a *potassium chloride* solution into the jugular vein, carotid artery, or ventricular cavity would often cause experimental fibrillation to cease and a normal ventricular beat to return, especially if the injected material was spread through the myocardium by massage and a calcium chloride solution was then injected to enhance the vigor of contraction.[27,71,187,188] *However*, although potassium ions decrease conduction and abolish fibrillation, they also

survive, and generally in the presence of extensive collateral development

Ventricular Fibrillation —The occlusion of a coronary artery or a branch in man (or experimentally, in animals) accounts for the great majority of cases of ventricular fibrillation In addition, it can follow an adequate electrical stimulus applied either directly to the heart or to the body surface,[87,19] chloroform anesthesia,[100] the administration of epinephrine in association with barbital or cyclopropane anesthesia,[109,18] or benzol inhalation, the administration of various drugs in toxic doses such as digitalis, ouabin potassium *chloride, quinidine sulphate and papaverine,*[183,184,185] and mechanical insults to the heart

Not all species are equally susceptible In man, the dog, sheep, and goat, ventricular fibrillation occurs readily is not spontaneously reversible, but can be made to disappear by artificial means In the frog and turtle, this condition probably does not occur spontaneously and is difficult to induce but, following its occurrence spontaneous recovery invariably occurs In the mouse rat, cat, rabbit, monkey and fowls it is easily induced but spontaneous recovery is the rule

This condition which was first described by Ludwig in 1850 has been *studied intensively to the present time* The *force* by means of which blood is ejected from the ventricular cavity arises from the essentially simultaneous contraction of all the muscle fibers of the ventricle During fibrillation the fibers still contract but in an unorganized and disassociated fashion and in small areas, with only a few fiber groups contracting at any one time When ventricular fibrillation occurs there results a precipitous decrease in systemic and pulmonary pressures an increased systemic venous pressure, and death follows within a few minutes During the first few seconds of the process the ventricle undergoes a few undulatory contractions which resemble premature contractions A fair degree of coordination *still exists and rather large muscle blocks are excited in sequence* Later successive stages of incoordination set in characterized by progressively more frequent contraction waves involving progressively smaller areas At first these areas although out of phase, execute powerful contractions but very soon the ventricular surface is broken up into a multiplicity of very small independently contracting areas of groups of muscle fibers all out of phase Finally after a period of time varying from five minutes or so to half an hour all *observable activity ceases in the ventricle*[190] Despite the fact that no external work is done, the fibrillating heart perfused with

is of great value By trial in open-chest dogs the strength of the weakest current stimulus just sufficient to cause fibrillation the so-called fibrillation threshold was found Using this method the fibrillation threshold was greatly reduced during experimental coronary occlusion[14] the drugs quinidine procaine adrenaline and papaverine exerted a protective action (increased fibrillation threshold) against the induction of ventricular fibrillation[13,14] by electrical means while therapeutic doses of digitalis did not change the threshold[14] However no drug or procedure even though it may raise the fibrillation threshold has been found which renders it impossible to induce ventricular fibrillation by electrical stimulation during the vulnerable period It is also doubtful that in coronary occlusion in which fibrillation is most feared that a drug can reach the ischemic area in sufficient concentration to be effective

Collateral Development – From the diagram in figure 12 p 33 it is obvious that the coronary circuit is intricate and complex The regions of the normal heart are safeguarded by many actual and potential sources of supply of blood (1) from the normal coronary arteries (2) from intercoronary arterial and venous anastomotic connections (3) from arterio-sinusoidal and arterio-luminal vessels connecting the coronary arteries and the lumina of the ventricles (4) from Thebesian veins connecting the coronary veins and heart cavities and (5) from extracardiac vessels connected to the coronary arteries and veins However their mere existence and the ability to inject them in dead hearts does not signify that any or all are functionally adequate and the fact that occlusion of a small branch of a coronary artery may so often result in an infarct and/or death indicates an inadequate functioning of these apparent safeguards to the myocardial blood supply

As will be seen physiological studies have clarified to some extent the mechanism by which the myocardium is nourished in the presence of acute or chronic coronary artery or vein obstruction and how it may be aided however the ultimate solution of the problem of development source and determinants remains to be elucidated

Dynamic studies following acute and chronic obstruction of a coronary artery in which studies have been made of the volume character and source of the collateral or retrograde flow as well as the pressure head under which it enters the peripheral end of the centrally occluded coronary artery and the extent to which it replaces the normal blood supply of the occluded coronary artery have been most helpful

In the study of collaterals the coronary arteries may be constricted or occluded abruptly or gradually For chronic exper

depress contractility and the activity of pacemakers while calcium awakens many foci of excitation so that such hearts easily revert to the fibrillatory state Later, Wiggers[189] with Wegria revived, modified, and improved the countershock method of Hooker, Kouwenhoven and Langworthy [3] and found that by the application of 60 cycle alternating current of about 3 amperes in intensity and 0 1 *second in duration through padded electrodes applied to the fibrillating* ventricles defibrillation occurred in about 100 per cent of trials in dogs whose ventricles had been previously fibrillated by applying a small shock during the vulnerable period The author has found that a normal beat may be reestablished by such a procedure after eighteen to twenty minutes of fibrillation, provided there is an occasional massage during this period

There are formidable barriers to the practicability of the use of the counter-shock method for the revival of human ventricular fibrillation during occlusion The human heart is considerably larger than that of the dog, and in the large dog hearts it is often difficult to obtain sufficient current penetration to stop fibrillation in the depths of the myocardium In addition the counter shocking technique is most effective with the electrodes in close proximity to the myocardium and within the first few minutes after fibrillation Since an external current of sufficient intensity applied to the chest wall would be damaging effective use of the counter shock method would entail exposure of the fibrillating heart under artificial respiration *for electrode application an unduly long and noxious procedure* at the end of which many of the body organs would have undergone irreversible injury as the result of the sustained anoxia Finally the fact that most cases of human ventricular fibrillation occur after coronary occlusion renders the successful application of present methods even more difficult, for as already indicated experimentally in dogs it is generally impossible to revive such a heart from ventricular fibrillation Any great hope for success along these lines is probably restricted to an occasional case of electrocution or to a patient who develops fibrillation from an extracoronary vessel cause during the course of thoracic surgery From this approach the method has *been used successfully by Beck*[6] *in reviving human* hearts from true fibrillation

Since defibrillation of a heart with coronary occlusion is generally not practical with present methods efforts are being directed toward agents that might prevent fibrillation While no one agent has been shown to obviate fibrillation the procedure devised by Wiggers and Wegria[193] in 1940 to test the effect of different factors on the tendency of ventricles without coronary occlusion to go into fibrillation

TABLE 11 —CHANGES IN PERIPHERAL PRESSURE AND FLOW IN THE CORONARY ARTERIES

Expt No	Duration of Occl	Blood Pressure mm Hg	Peripheral Co Pressure mm Hg	Peripheral Co Flow cc min	Comment
		Left Descending			
11	30 sec	10[illegible] 56 (Carotid)	30 20	[illegible] 0	
	30-60 sec	103 53 (Carotid)	[illegible]	0	Left circumflex clamped
	[illegible] min	65 (Mean Carotid)		4	
	[illegible] min	100 (Mean Carotid)		[illegible] 8	Aorta clamped
	[illegible] min	6[illegible] (Mean Carotid)		3 [illegible]	
8	[illegible] min	118 94 (Carotid)	31 10	1 9	
	6 hours	98 74 (Carotid)	31 [illegible]	[illegible] 5	
9	13 min	[illegible] (Mean Carotid)		3 4	
	48 hours	85 (Mean Carotid)		[illegible] 8	
10	[illegible] days	10[illegible] [illegible] (Carotid)	[illegible]	8 5	
	[illegible] days	13[illegible] 10[illegible] (Carotid)	104 7	[illegible] 0	Aorta clamped
6	10[illegible] days	11[illegible] [illegible] (Carotid)	85 [illegible]	14 0	
[illegible]	Many Expt	10[illegible] 6[illegible] (Carotid)	[illegible] 38	[illegible] 0	
		Left Circumflex			
	[illegible] min	110 88 (Carotid)	[illegible] 18	<1 0	
1	6 days	134 10[illegible] (Carotid)	10[illegible] [illegible]	[illegible] 0	
	1[illegible] days	111 [illegible] (Carotid)	[illegible] 31	8[illegible] 0	
	10[illegible] days	110 [illegible] (Carotid)	8[illegible] 4	[illegible] 0	
	4[illegible] days	104 [illegible] (Carotid)	7[illegible] 44	60 0	
[illegible]	Many Expt	10[illegible] 60 (Carotid)	[illegible] 38	58 0	
		Right Coronary			
1	[illegible] min	140 9[illegible] (Carotid)	30 [illegible]	<1 0	
14	98 days	10[illegible] [illegible]0 (Carotid)	48 37	1[illegible] [illegible]	
1	40 days	80 50 (Carotid)	11 10	[illegible] 1	
16	360 days	93 [illegible]0 (Carotid)	[illegible] 60	41 0	
	360 days	13[illegible] 104 (Carotid)	110 9[illegible]	80 0	Aorta clamped
[illegible]	Many Expts	10[illegible] 71 (Carotid)	68 51	[illegible] 0	

Averages based on coronary occlusion of one week or more

during diastole that further reduction in diastolic filling by ligating a coronary collateral is insufficient to affect diastolic pressure and the peripheral pulse pressure [49,50]

The above indicated fact that an increase in blood flow through a potentially infarcted area follows an augmented venous return provides a partial basis for the rationale of the use of blood transfusions following coronary occlusion in humans [1] However the value of such an increase in coronary collateral blood flow must be offset in part at least by the resultant increased work load placed upon the heart

Despite the presence of a small collateral blood supply to the potentially infarcted area the myocardium normally fed by the occluded coronary artery becomes ex anotic after approximately one minute of occlusion and expands with each heartbeat rather than shortens (See Fig 66) Tennant and Wiggers[169] were the first to

iments, an artery may be tied off abruptly but more gradual constriction of the lumen may reduce the incidence of ventricular fibrillation, minimize infarction and augment collateral development. The use of adjustable mechanical, or osmotic clamps or the application of tight-fitting bakelite rings or cellophane bands to the artery will ultimately lead to complete coronary occlusion.[135-137] Unfortunately by none of these methods can the time of complete occlusion be known, nor can the per cent reduction in flow be predicted even if the extent of local reduction in vessel lumen were known. As in other vessels, the effectiveness of a given localized constriction in reducing flow may be large or small and will vary in inverse relation to the peripheral resistance of the vascular bed and lumen area of the constricted segment and in direct relation to the axial length of the constricted area, flow velocity and blood viscosity.[157]

No entirely adequate method is available to measure the extent of development of the collateral coronary bed in acute or chronic experiments after occlusion of a coronary artery. An indication of intercoronary collateral development can be demonstrated experimentally by measurement of retrograde flow and/or pressure from a severed main coronary branch,[50] by ultimate injection of the heart with radiopaque material,[105] or by its perfusion after death with *radioisotopes or graduated glass spheres*.[137,138]

Some of the immediate and delayed effects of coronary occlusion in the anesthetized, open chest dog are illustrated in Table 11. Immediately following abrupt occlusion of a main branch of a coronary artery *the retrograde coronary flow approximates 0.5 to 0.8 cc./min. in* different sized dogs and is relatively constant in any one dog for a few hours.[35,50] This blood is bright red and has the same oxygen content as blood in the systemic arteries. As to be expected, the pressure in the coronary artery distal to the point of occlusion falls greatly, being in the range of 30/20 mm. Hg. It is obvious that the occluded bed is *incompletely filled*. *The retrograde flow and pressure values are* easily and largely increased by augmentation of venous return and aortic blood pressure. Measurements of retrograde flow during temporary clamping of the other coronary arteries indicate that the latter are the major source of flow and when both are temporarily ligated, essentially no retrograde flow could be measured distal to the ligatures (*See* Table 2, *p. 81*). *However*, the peripheral coronary pressure does not decline following clamping of such potential sources of retrograde flow. The most probable explanation for the failure of the peripheral coronary pressure to decrease in the latter instance is that *after* occlusion the coronary bed is so poorly filled

TABLE 11 — CHANGES IN RETROGRADE PRESSURE AND FLOW IN THE CORONARY ARTERIES

Expt No	Duration of Occlusion	Blood Pressure mm Hg	Peripheral Cor Pressure mm Hg	Peripheral Cor Flow cc m	Condition
		Left Descending			
11	10 sec	10 86 (Carotid)	30 0	0	
	30-60 se	103 83 (Carotid)	29 20	0 7	Left circ in fl x 1 n ped
	? min	65 (Mean Carotid)		4	
	20 min	100 (Mean Carotid)		5 8	Aortic clamp
	55 min	65 (Mean Carotid)		3	
8	35 min	115 94 (Carotid)	31 10	1 9	
	6 hours	98 4 (Carotid)	31	2 5	
9	13 min	1 3 (Mean Carotid)		3 4	
	48 hour	85 (Mean Carotid)		6 8	
10	7 days	10? 74 (Carotid)	68 ?	8 5	
	d ys	13 10 (Carotid)	104 ~	?4 0	Aortic clamp
6	10? days	11? 68 (Carotid)	85 ?1	34 0	
A	Many Expt	10 ?? (Carotid)	8 38	?5 0	
		Left Circumflex			
	min	110 88 (Carotid)	? 18	<1 0	
1	6 days	134 106 (Carotid)	105 54	? 0	
	?9 day	111 47 (Carotid)	69 31	81 0	
	106 days	110 8 (Carotid)	8? 47	4 0	
	46 day	104 54 (Carotid)	77 44	60 0	
A	Many Expt	107 60 (Carotid)	? 38	58 0	
		Right Coronary			
13	5 min	140 9 (Carotid)	30 4	<1 0	
14	98 days	10 0 (Carotid)	48 37	12	
1	40 days	80 50 (Carotid)	11 10	0 1	
1?	60 days	93 0 (Carotid)	75 60	41 0	
	360 day	13 104 (Carotid)	110 ?	80 0	Aortic clamp
A	Many Expt	10 71 (Carotid)	68 51	?7 0	

A erage based on c a y occlu on of one week or mor

during diastole that further reduction in diastolic filling by ligating a coronary collateral is insufficient to affect diastolic pressure and the peripheral pulse pressure [35 5]

The above indicated fact that an increase in blood flow through a potentially infarcted area follows an augmented venous return provide a partial basis for the rationale of the use of blood transfusions following coronary occlusion in humans [18] However the value of such an increase in coronary collateral blood flow must be offset in part at least by the resultant increased work load placed upon the heart

Despite the presence of a small collateral blood supply to the potentially infarcted area the myocardium normally fed by the occluded coronary artery becomes cyanotic after approximately one minute of occlusion and expands with each heartbeat rather than shortens (See Fig 66) Tennant and Wiggers [19] were the first to

call attention to this important fact. In hundreds of occlusions, we have never seen an instance in which shortening of muscle fibers during systole returned spontaneously, or that this could be induced by alteration of systemic blood pressure (but *see* Corday *et al.*[19]). On the other hand, the fact that the area bulges during systole does not necessarily mean that the myocardium is not viable. It is more probable that it is attempting to shorten, but the force exerted is so weak as to be over balanced by the intraventricular pressure which distends it. This is rendered likely by the fact that with time only small areas of scarring develop.

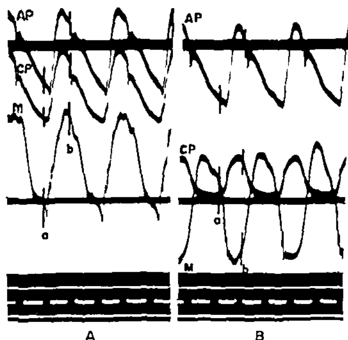


Fig. 66. – Reproduction of segments from record showing in A normal contraction and in B failure of contraction after ligation of ramus descendens anterior and the coronary sinus. AP, aortic pressure; CP, coronary pressure; M, myogram; a–b, approximate duration of systole; rise of curve M indicates shortening of muscle fibers. Time 0.2 sec. (Gregg *et al.*[11])

Despite the small collateral blood flow and bulging of the myocardium with each systole, the aortic blood pressure and cardiac output may be sustained or increased[16] and the right atrial pressure may not rise.[91] However, the more usual occurrence is that the heartbeats become immediately hypodynamic, characterized by decreased pressure amplitudes and a significant reduction in systolic discharge and the interval of systole. In consequence of the reduced systolic output, systolic and diastolic pressures fall. These effects are promptly compensated for by an increase in diastolic

size and a rise of initial tension which restores to normal the systolic pressure in the left ventricle as well as the duration of contraction. It is presumed therefore that the remainder of the ventricle with its normal blood supply is compensating for the potentially infarcted myocardium.

In long continued ligation of a coronary artery or a branch in an otherwise normal heart the flow of blood from the cannulated peripheral end of the artery becomes quite large. In the left coronary rami large increases in flow have never failed to be established. Typical values are given in Table 11. The retrograde blood flow starts to increase within a few hours, may double within forty-eight hours and is 3 to 4 times the control level within a week. In the left descendens the values have varied from 6 to 100 cc per minute; in the left circumflex from 32 to 84 cc per minute. In the right coronary artery the peripheral flows are generally less than in the left (at the same aortic blood pressure) and have varied from 0.1 to 50 cc per minute. Within a few weeks the flows approximate the preocclusion values for the normal rate of inflow in that coronary artery or branch. The observations that the retrograde blood has the same content of oxygen and carbon dioxide as that in a systemic artery leaves no room for doubt that the collateral circulation established is on the arterial side of the coronary capillary bed.

Associated with the augmented retrograde blood flow after long sustained coronary artery occlusion is a gradual and ultimately large elevation of the systolic and diastolic pressures in the peripheral end of the occluded coronary artery.[34, 50, 106] These trends are indicated in Table 11. The peripheral coronary pressure immediately after coronary artery ligation approximates 30/20 mm Hg. No significant change occurs generally for the first few days despite an increase in retrograde blood flow. However after a week or so (expt 10) the peripheral coronary pressure is elevated considerably. The average peripheral pressure including many experiments not in Table 11 approximates 82/38 mm Hg in the descendens, 72/38 mm Hg in the circumflex and 68/51 mm Hg in the right coronary artery. Ultimately many of the values approximate the central pressure in the unoccluded coronary artery.

As to be expected acute alterations in cardiac hemodynamics such as increased venous return or elevation of blood pressure in the presence of a chronically occluded coronary artery result in a corresponding augmentation of peripheral coronary pressure and blood flow. Typical examples of the augmentative effect of increased aortic pressure on peripheral coronary pressure and flow are illustrated in Table 11.

Although such findings definitely indicate that a new arterial blood supply of good volume and under a good pressure head does develop spontaneously in a potentially infarcted area, it gives no information as to whether it is sufficient in quantity to nourish the muscle mass previously rendered ischemic It is improbable that flows of such magnitude as were obtained experimentally against atmospheric pressure exist when the chronically occluded coronary artery is not permitted to bleed As already indicated in figure 66 immediately after occlusion of a coronary artery, the myocardium fed by it expands with each heartbeat rather than shortens Hence the conclusion is justified that any persistence or recurrence of contraction in hearts with complete coronary occlusion is caused by the appearance of newly functioning collaterals In most hearts with occlusion of a coronary artery or branch small areas of scarring

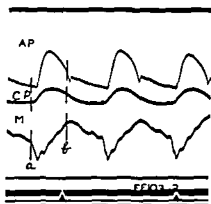


Fig 67 —Reproduction of record showing systolic shortening in myocardial area of a chronically occluded ramus descendens M myogram vertical intercepts duration of systole AP aortic pressure CP coronary pressure a b systolic shortening Time 1 0 sec (Gregg *et al* [50])

are present but in all dogs (except one) that have survived this procedure the potentially infarcted area was visibly shortening during systole A typical myogram taken from the myocardial region of the left descendens after one hundred six days of occlusion is contained in figure 67 The record shows systolic shortening (a b)

Although such volume flows of arterial blood are apparently adequate for the metabolic needs of the potentially infarcted myocardium it should be emphasized that there is a considerable natural variation in the ability of such anastomotic circuits to develop in different dogs The mortality accompanying these coronary operations is considerable Those dogs which survive complete occlusion

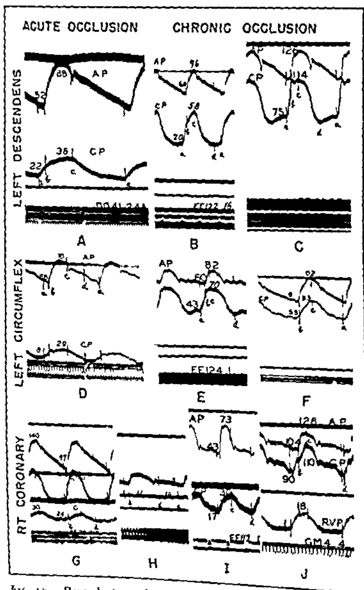


FIG [illegible] Reproduction of segments of records illustrating the effects of long continued coronary artery occlusion on peripheral coronary pressure. A–D (normal peripheral coronary pressures in descendens, circumflex and right coronary arteries respectively. Other curves after chronic coronary artery occlusion. Descendens B, C, circumflex E, F, right H, I, J. AP aortic pressure. CP peripheral coronary pressure. a, b, c, d vertical intercepts to facilitate curve reading. Time 0.02 sec, 0.2 sec. (Gregg et al [80])

of a coronary artery, without doubt, represent a select group naturally endowed with a high resistance toward this type of procedure

Studies have shown that the pressure curves obtained from the peripheral ends of major coronary rami shortly after their occlusion are fairly constant as regards form, magnitude, and time relations, with the exception of that in the right coronary artery, in which the magnitude is less [50] Typical contours for the descendens and circumflex branches of the left coronary and for the right coronary artery are illustrated in the left-hand side of figure 68 Simultaneously with the onset of the isometric contraction period at *a* the peripheral pressure starts to rise, and then continues more slowly to the opening of the aortic valves at *b* to reach a peak value at the beginning of protodiastole at *c*

A careful study of a large number of curves from dogs with long continued occlusion of their coronary arteries has shown that the pressure curves in their peripheral ends are generally altered but not according to any consistent pattern In figure 68 are presented peripheral pressure curves obtained in the different coronary arteries for comparison with the curves from the corresponding vessel immediately after occlusion No single pulse pattern or set of ordinate values exist The obvious differences in the patterns in some of the chronically occluded coronary arteries as compared with those in acutely occluded arteries are that the diastolic pressure which normally declines or remains constant during the latter part of diastole may rise and the summit which normally occurs late in systole can come much earlier or it may remain normal As a result of these changes the peripheral pressure curve may be strikingly similar to that of the central coronary pressure curve (I J) others more nearly resemble an intraventricular pressure curve (C, E) while still others are similar in timing and contour although greater in magnitude to the curve obtained immediately after coronary ligation (B I) In an occasional dog the myocardium is infarcted does not shorten during systole and a peripheral pressure pulse is just discernible (H) Of these pulses the most usual pattern is that which is very similar to the peripheral coronary pressure pulse obtained soon after vessel occlusion The ventricular type occurs less frequently, while in only two experiments have coronary pressure curves scarcely distinguishable from the aortic been found

The collateral bed may consist of many small or large superficial connections or it may be made up of small or large size vessels which are deeply buried in the myocardium Injection studies indicate that these anastomotic connections are mainly in the epicardial region [13] Since the peripheral coronary pressure rises and

falls in any one experiment with concordant changes in retrograde flow and its contour is limited to definite patterns, examination of them should reveal, in part at least, the source and time of entry of blood and pressure into the occluded coronary artery. In two experiments (Fig. 68 F, J) it is quite certain that most of the peripheral pressure head and therefore retrograde blood flow comes from an artery near the aortic valves, for the systolic and diastolic values of the peripheral pulse approach the aortic pressure simultaneously recorded, most of the rise occurs after opening of the aortic valves and even an incisura is present, or in other words, the peripheral coronary curve parallels in all respects the aortic. It is therefore logical to assume that the connections between this artery or arteries and the vascular bed of the occluded coronary are of good cross section and superficially located in the myocardium. Actually this was found to be the case, for roentgenogram of one of these injected hearts (J) showed a large vessel connecting the occluded artery with the circumflex.

The transition from the normal peripheral pulse representative of that artery (Fig. 68 D, G) to one resembling the aortic or central coronary pressure pulse must mean that the peripheral pulse is no longer a partial measure of the intracoronary resistance, but rather represents the head of pressure entering the area from some artery, either coronary or extracoronary. Viewed in this light, namely, that the peripheral coronary pressure has now become a central one, and since we have no reason to suppose that the peripheral coronary resistance has materially changed from the normal (unpublished experiments), it would be predicted that the phasic blood flow in it would be similar to that in the unobstructed left and right coronaries, that is, a greater volume flow in the left during diastole as compared to systole, and in the right a greater systolic than diastolic flow (See Fig. 36, p. 93).

Of the remaining coronary pulses, none are similar to a known arterial pulse (except for their high systolic and diastolic values). Since the source is known to be largely some artery, as demonstrated by clamping the other coronaries, the question arises why so few of the curves resemble an arterial pulse. It is quite likely that the differences in configuration of the peripheral coronary pulses are caused by the fact that in most the collateral architecture and location are such as to distort the curve, i.e., they consist of many small superficial connections or they are of small or large size but deeply buried in the myocardium. This concept has been borne out by injection studies.

From an examination of such pressure curves found in chronically

occluded coronaries, it is believed that most of the flow through the vascular bed of the occluded coronary is at a minimum during systole for most of the rise of the peripheral pressure precedes the opening of the aortic valves, and is at a maximum during diastole for the diastolic pressure after isometric relaxation (when the capacity of the vascular bed is presumably constant) is either rising or falling. This view is substantiated by optical records of the phasic blood flow *into the occluded coronary artery*.

Anatomical considerations suggest several source possibilities for the newly established collateral circulation. Gross evidence of the development of extensive intercoronary arterial collaterals within the heart has been shown roentgenographically with the injection of a radiopaque medium.[105,106] Anastomoses exist between the coronary arterial tree and extracoronary arteries reaching the heart along the course of the great vessels and anatomical pathways occur from the cavities of the heart to the centrally occluded segment by the channels described by Wearn.[151] Of these possibilities only one, the possible role that the intercoronary communications might play in

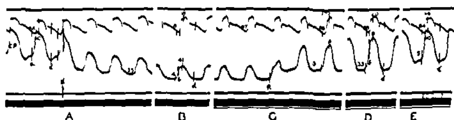


Fig. 69.—Reproduction of segments of a continuous record illustrating the immediate effects of left circumflex occlusion on the peripheral coronary pressure in the chronically occluded ramus descendens anterior. A, normal control with circumflex ligation at X. B, same but 18 heartbeats later. C, circumflex release at R. D and E, taken 30 and 60 seconds later. (Gregg *et al*.[50])

the collateral circulation has been subjected to direct experimental investigation. The method used to obtain this information consisted in clamping the other two coronary arteries, either separately or together, while the peripheral pressure and flow were being recorded in the coronary chronically occluded. The immediate and stabilized changes produced in different coronary arteries are illustrated in detail in figure 69 and Table 12.

In the curves of figure 69, the ramus descendens had been ligated for fifty days. The first two heartbeats in segment A represent the normal aortic pressure 113/86 mm. Hg and the pressure 100/61 mm. Hg in the peripheral end of the chronically occluded descendens

TABLE 3.—SOURCE OF RETROGRADE PRESSURE AND BLOOD FLOW IN CHRONICALLY OCCLUDED CORONARY ARTERIES

Artery Chronically Occluded	Artery Acutely Occluded	Per Cent Reduction Peripheral Coronary Signal		Per Cent Peripheral Coronary Collateral		Per Cent Extracoronary Collateral Flow
		Hg	Flow	Hg	Flow	
Descendens	Right		3 10	6	55 74	18
	Left circumflex	55	5 64			
	* Right and left circumflex			60	49 50	34
Left circumflex	Right	19	15 11	60	48 48	34
	Descendens	4	33 3			
	* Right and descendens			64	59 54	30
Right	Descendens		30 33	9	[illegible]	5
	Circumflex	75	61 63			
	Descendens and circumflex			9	3 5	1

* Arteries simultaneously occluded

The normal retrograde flow was collected from the coronary vessel in a bottle of suitable size to avoid any significant pressure change. The bottle was connected by large rubber tubing to a large segment capsule which recorded optically. The control retrograde flow measured 52 cc per minute. At X the left circumflex was suddenly occluded and the peripheral pressure decreased in three heartbeats to 56/23 mm Hg. After 15 heartbeats (only the last beat shown here) the peripheral coronary pressure attained a new and final equilibrium of 41/14 mm Hg and the back flow was 10 cc per minute. About 5 heartbeats later in segment 4 the left circumflex was released at R and the peripheral coronary pressure immediately rose to 84/34 mm Hg in C. In L, recorded sixty seconds later, the peripheral pressure of 110/55 mm Hg is back to the control level, while the back flow at this time is 53 cc/minute. While the role of the right coronary as a collateral source for the descendens was not determined in this experiment, its maximum contribution, together with all remaining collaterals, could not exceed 19 per cent.

Similar trends in pressure and flow occur after chronic occlusion of the left circumflex. After chronic occlusion of the right coronary artery, the sudden clamping of the descendens gives but a very small reduction in peripheral pressure and flow, but circumflex occlusion results in large pressure and flow reductions.

These figures show that when a coronary artery has been chronically occluded and both of the other major coronary rami are temporarily clamped separately and acutely, the sum of the flow reduction may not approximate 100 per cent. Similar results follow simultaneous closure of the remaining coronary rami. All our data on

this point are briefly summarized in Table 12. In the right coronary artery chronically occluded essentially all the retrograde flow comes from the other coronary arteries (most from the circumflex), while in the descendens, only 62 per cent comes from the right (7 per cent) and circumflex (55 per cent) and in the circumflex only 66 per cent comes from the other coronaries (right 19 and descendens 47 per cent). This leaves a considerable residual flow in the left coronary still to be accounted for. This portion of the collateral flow could arise from small coronary artery branches central to the point of ligation or clamping of the coronary arteries, or it could have a true extracoronary origin. The source has not been determined.

If intracardiac sources of collateral blood supply are insufficient extracardial anastomoses also become evident and sizeable extracardial communications can be demonstrated. Under the most favorable conditions the major portion of the coronary artery system can apparently be occluded with minimal or no infarction in those dogs that survive.[1]

The factors which control the rate and extent of coronary arterial collateral development are not well known. The potential mechanisms for collateral reactions are the opening of pre-existing, but nonfunctioning collaterals by an increased differential pressure, metabolites and nerve action, or the formation of new collaterals. Immediately following coronary occlusion the differential pressure between the vascular bed of the occluded coronary and non-occluded coronary artery is greater throughout the cardiac cycle and may account for the opening of collaterals. Whether the subsequent further increase in retrograde flow is through the same collaterals or through newly formed channels or whether the latter ever develop has never been determined.

Although in the normal heart, there is considerable variation in the number and size of connections between the coronary arteries the connecting channels are quite small (but extend up to arteriolar size) and can be important only as a potential source of blood. In general the more gradual the rate of experimental occlusion of a coronary artery the smaller the mortality rate and the greater the extent of collateral development.[8,11] Following experimental occlusion of a coronary artery or ramus the interarterial communications enlarge considerably (up to 10 times the diameter of those in the control dogs) and increase greatly in length as is evidenced by their striking tortuosity. These vessels do not acquire an arterial coat but are similar to a dilated thin-walled arteriole.[105] Similarly in the hearts of elderly humans obstruction to the normal coronary artery flow by arteriosclerosis leads to the development of inter

coronary anastomoses of 40 to 200 microns in diameter. Their presence is not related to age for these collaterals are not present in the hearts of senile patients when little or no arteriosclerosis is present.[1]

The behavior of the collaterals of the coronary arteries following occlusion contrasts with that of the femoral and carotid arteries (*See* Table 11 for ordinate values and Figure 70 for the peripheral

FEMORAL ARTERY OCCLUSION

CAROTID ARTERY OCCLUSION

Fig. 70.—Records showing development of retrograde pressure in acutely occluded femoral (upper records) and carotid arteries (lower records). PFP, peripheral femoral pressure. CFP, central femoral pressure. PCP, peripheral carotid pressure. CCP, central carotid pressure. Time 0.2 sec. (Eckstein *et al.*[34])

pulse patterns). In the coronary arteries, as already described, the immediate evidence of functioning of the collaterals is small and the development of retrograde pressure and flow and the reestablishment of systolic shortening of the myocardium is very slow and may take one to two months before its full development. However, although immediately after occlusion of a femoral artery the retrograde pressure and flow drop to low values and the pressure pulse disappears, within one minute or less a peripheral pulse appears and it and the retrograde flow increase rapidly for one to two hours and then rise more slowly for days and weeks. Following carotid artery ligation, the peripheral pulsation does not cease and the retrograde flow and pressure are considerable, start to increase in a matter of seconds and reach large values very quickly. These experiments throw new light on the coronary artery collaterals and emphasize the importance of the time element. They show why, despite the *apparent safeguards to the blood supply of the myocardium, the* occlusion of a coronary artery may more often than not lead to an infarct and death. The relatively long time necessary for the establishment of maximum functioning of the coronary collaterals may be regarded as an indication of the optimum length of rest necessary for patients with coronary occlusion.

It is of interest to examine the possible role of the Thebesian and luminal vessels in hearts in which either the coronary arterial or cardiac venous system is insufficient. It is conceivable that the luminal vessels could be important, particularly if they could serve as arterial channels from the left ventricle to the myocardium during left coronary artery occlusion or as venous channels for the whole myocardium in the presence of extensive superficial vein occlusion. Known observations are conflicting and any conclusion is difficult. Regarding the first situation with temporary functional separation of one or all coronary arteries from the aorta no blood flow from the ventricles into the coronary arteries or superficial venous system could be demonstrated and the hearts did not survive.[49,163] Essentially complete occlusion of the coronary arteries in humans has been found at autopsy,[96] but the presence and extent of development of extracardial arterial collaterals not indicated. When dye is injected into the right ventricle in acute experiments extensive capillary injection occurs if right ventricular pressure is artificially made to exceed left ventricular pressure. However the anterior cardiac veins were not excluded as a vascular portal of entry for the dye.[36] Regarding the second situation with acute closure of all grossly visible anterior cardiac veins or the coronary sinus a considerable reduction in right and left coronary inflow (especially the

right) was observed by the author More recently, Shipley has demonstrated that the coronary inflow and aortic pressure in some hearts may be greatly reduced by sinus closures Although the heart following acute closure of both the coronary sinus and anterior cardiac veins becomes exceedingly hemorrhagic and tends to become progressively weaker such hearts may survive up to at least two hours Dogs in which both superficial venous systems have been chronically occluded in a two-stage operation have survived for a period of months The latter is suggestive evidence that all

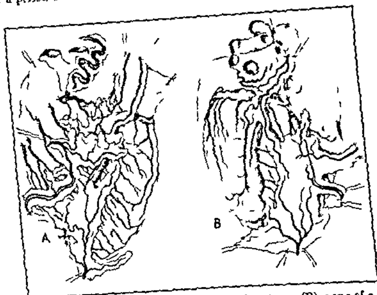


Fig 71 —Drawings of the anterior (A) and posterior (B) views of a dog heart following chronic ligation of the anterior cardiac veins (4 months) and coronary sinus (2 months) showing the extracardiac superficial venous channel. Heart injected in situ post mortem through an extracardiac vein with a gelatin Evans Blue mixture Note injection of the superficial veins of both ventricles and of the extracardiac veins (Gregg et al[4])

venous drainage now occurs by way of luminal vessels However that significant drainage occurred through such a route could not be verified since at post mortem examination these hearts exhibited numerous superficial cardiac veins of considerable size which were not previously evident and several large extramyocardial venous anastomoses the aggregate cross-section of which might well have been adequate for the venous drainage of the entire heart (Fig 71) Until such intra and extracardial arterial and venous collaterals which appear with coronary arterial or venous ligation have been successfully removed or otherwise excluded as

flow channels, a statement as to the utilization of Thebesian channels in diseased hearts is not warranted

Brief mention should be made of an hypothesis of reflex coronary vasoconstriction which has been advanced as an explanation of sudden cardiac death from coronary occlusion "The sudden death of a patient with infarction of the myocardium is due to reflex coronary vasoconstriction whose stimulus is the infarct whose afferent path is the cardiosensory innervation and whose efferent path is the vagus The result of this reflex vasoconstriction in a susceptible person is fatal ventricular fibrillation "[98] If true, then the associated vasospasm must produce and maintain ischemia in the presence of one of the most powerful dilators known, anoxia In support of the view, it is advanced that the mortality from ligation of a coronary artery is greater in unanesthetized dogs as compared to anesthetized dogs [104] bilateral stellate removal improves survival rates greatly in unanesthetized dogs [107] and various drugs, atropine papaverine xanthines and aminophyllin decrease the mortality rate [99, 103, 113] While drug action and cardiac nerve section may enhance survival this does not prove that the mechanism of action is the release of an associated coronary vasospasm which has reduced coronary inflow in other non occluded coronary arteries Such a view is predicated on the necessary experimental proof that cardiac nerve stimulation can lead to ventricular fibrillation and that coronary inflow directly measured in the non occluded coronary artery decreases after occlusion of a coronary artery or ramus Actually in anesthetized dogs the coronary flow is generally found to increase in the non occluded coronary artery or ramus [43, 54]

To increase the natural compensatory collateral circulation subsequent to narrowing or occlusion of a coronary artery various surgical and medical means have been tried in experimental animals

Surgical Treatment — Many dogs do not survive abrupt or gradual experimental coronary occlusion In addition to gross coronary insufficiency it has been suggested that the ultimate cause of death generally ventricular fibrillation may stem from small zones of myocardial anoxia which are highly irritable and this is not necessarily related to a failing heart or to gross coronary flow inadequacy This is in keeping with the findings of Harris and Rojas that the ectopic impulses leading to ventricular fibrillation generally arise from the partially ischemic zone bordering on the infarcted area [55] Accordingly surgical removal of these danger zones has been tried In addition if small amounts of blood via collaterals could be made to enter these zones at the edge of an occlusion it might prevent ventricular fibrillation and eliminate scar tissue formation through

muscle preservation Accordingly attempts have been made to subsidize surgically the natural compensatory ability of cardiac tissue to develop collaterals

Regarding the first possibility excision of potentially infarcted area some time after closure of the coronary artery feeding the area has lowered considerably the experimental mortality from coronary occlusion[115]

Application of various tissue grafts has been used to promote extracardial communications epicardial or pericardial inflammation has been produced to foster intercoronary and extracoronary communications through mechanical or chemical irritation[4] The tissues applied to the myocardium include pericardium pericardial fat skeletal muscle from the chest wall omentum and lung The foreign irritants used to induce adhesions within the heart and with surrounding structures include aleuronat asbestos talc Dakins solution powdered bone and the application of a dental burr When these substances and procedures were used experimentally before or during partial occlusion of a coronary artery or major ramus new vascular communications could be demonstrated with dye or radiopaque material injection

Opinion based upon physiological experiments is divided as to the functional role played by such channels[5,15] The size of the collateral bed in cleared hearts is enhanced the size of infarcts is in general reduced and there is a considerable reduction in mortality with all of these procedures In the background is the presence of naturally developing collateral which although not always adequate make interpretation difficult While these results are encouraging especially the survival figures it does not necessarily follow that the better survival rate stems from an increased blood flow to potentially infarcted areas for no crucial evidence has ever been advanced that this is the case In most instances of coronary occlusion death results from early ventricular fibrillation It could well be that the better survivals arise from the increased fibrillation threshold which many of these procedures might possibly experimentally induce[5] As a result time is gained for the spontaneous development of added collaterals which now sustain the heart Whatever the mechanism the fact remains that the procedures prolong life

Ligation of the coronary sinus or coronary veins has been tried as a means of increasing the blood supply to an area rendered ischemic by arterial occlusion[14,15] In acute experiments ligation of the coronary sinus increases greatly the pressure in the veins of the left ventricle limits left coronary inflow mildly or sometimes consid

flow channels, a statement as to the utilization of Thebesian channels in diseased hearts is not warranted

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inflow retrograde autoperfusion of the coronary sinus with the peripheral end of the left coronary artery open or closed failed to aid in restoring the aortic blood pressure and normal cardiodynamics

Although in acute experiments retrograde perfusion of the coronary sinus in the presence of an occluded left coronary ramus has not been demonstrated to be beneficial to the left heart the possibility remains that chronic application of this procedure might have positive benefit Beck *et al* [7] have reported that in chronic dogs a 3-stage operation consisting of coronary sinus ligation grafting of a systemic artery or new branch formed from the aorta into the coronary sinus followed by ligation of a coronary ramus has resulted in zero mortality and minimal infarction As already indicated reduction in mortality does not necessarily signify an improved coronary circulation To establish the latter it would be necessary to show that blood entering the coronary sinus had actually traversed the capillary bed of the left heart Although this is difficult to do experimentally indirectly it might be established by cannulating the anterior cardiac veins and showing that most of the blood entering the coronary sinus did not leave by way of the A C veins

These operations including the application of foreign irritants and grafts to the heart coronary sinus ligation and grafting of a systemic artery to the coronary sinus have been tried surgically on humans with coronary artery disease However the role of surgery in the relief of coronary insufficiency is difficult to evaluate although the operative mortality rate is relatively high symptomatic relief (decreased pain) and increased capacity for work often follow these procedures [7, 39, 40]

HYPERTROPHY

In man cardiac hypertrophy is generally associated with some pathological state such as hypertension aortic or pulmonary artery disease or it may be evident in long time residents at high altitudes who display no associated clinical or necropsy evidence of cardiovascular disease [149] It is believed by some that hypertrophy *per se* is a favorable compensatory mechanism which better enables the heart to cope with dynamic situations However there is no good experimental evidence to indicate that a heavy heart gives a better performance than a smaller heart

Hypertrophy has been successfully produced in animals but the experimental procedure has not been standardized or well defined In the rabbit or rat this state is easily induced as evidenced by an increase in heart weight/body weight and in muscle fiber diameter

erably and greatly increases retrograde flow distal to a coronary artery ligature.[46,47] However the ability of the myocardium distal to the ligature to contract is not maintained and the retrograde blood, in contrast to the small collateral flow normally present, is very dark containing only 3 volumes per cent oxygen. Thus it was concluded that acute occlusion of the major portion of the left heart's venous drainage does not aid the coronary circulation.

The high values for venous pressure in the coronary sinus and the augmentation of peripheral coronary artery pressure and retrograde flow which appear in the left coronary artery immediately after left cardiac venous ligation, decrease after a time interval (up to thirty days) to values but slightly greater than normal.[171] Such chronic venous ligation does not maintain shortening in the left myocardium if now a major coronary ramus is acutely ligated. If, after chronic coronary sinus ligation, a branch of the left coronary artery is chronically ligated, the coronary dynamics are identical with those following coronary artery occlusion alone, i.e., the retrograde flow is arterial, the retrograde flow and pressures are large and the myocardial area contracts. Although with this procedure there is a marked reduction in mortality and a slight reduction in the size of the infarct occurs,[6,51] no evidence has been obtained that chronic cardiac venous occlusion is of positive benefit to the functioning of collaterals.

Attempts to improve the coronary circulation by retrograde perfusion of the coronary sinus in dogs with a ligated coronary artery have not been too successful. In acute experiments in which arterial blood had been brought to the myocardium of the dog by a glass cannula connecting the coronary sinus with a convenient systemic artery, dogs survived up to twenty-six hours after ligation of a coronary artery.[143] The attempt was also made in an acute preparation to maintain or to restore systolic shortening in a left myocardial area whose coronary artery was occluded by perfusing the coronary sinus in retrograde fashion with arterial blood. Although blood could be observed entering the superficial venous systems of both ventricles, there was no evidence of systolic shortening in the potentially infarcted myocardium.[47] Visual inspection showed the anterior cardiac veins over the right ventricle to be greatly distended and, although no measurements were made, it was felt that most of the infused blood was draining by these channels which have been demonstrated to be so intimately connected with the venous drainage system of the left ventricle.[49] Similarly, Shipley *et al*[155] in acute experiments with the coronary sinus connected to a convenient artery, demonstrated that following stoppage of normal left coronary

heart The capillary concentration however shows a definite decrease which is caused by the enlargement of the muscle fibers As the fibers enlarge the capillaries are pushed further apart and the capillary concentration decreases in direct proportion to the increase in the diameter of the muscle fiber and heart weight The capillary concentration in these hearts averaging 2483 per square millimeter is appreciably lower than that for the hearts of normal adults or children [150] Cardiac hypertrophy induced in rabbits by aortic valvulotomy shows similar changes in the relation of growth of fibers capillary concentration and the relation of fiber-capillary ratio [158] Hypertrophy then differs from normal growth in that in the latter the capillaries multiply and keep pace with the muscle as it grows while in hypertrophy the capillaries do not multiply and per unit of muscle, actually decrease This is in line with the experimental observations (1) that human hearts perfused post mortem with kerosene under standardized conditions gave maximal flow values of 30 to 40 per cent less per gram of heart in hypertrophied hearts (300 to 600 grams) than in non hypertrophied hearts of the same age range [9] (2) in patients with essential hypertension the oxygen usage coronary O_2 A V difference and coronary flow per 100 grams of left ventricle per minute were not increased as compared to those values obtained in normal subjects [10] Since presumably left ventricular hypertrophy existed in these patients the observations suggest that the resistance in the left coronary bed is increased in the presence of essential hypertension However until further evaluation is made of the nitrous oxide flow method used interpretation must be reserved

The chemical changes in the heart in this condition are essentially unknown Shifts in the electrolyte pattern are presumed to be a sensitive indicator of tissue change In the rabbit the intra and extracellular electrolyte and fluid concentrations have a normal relationship in the hypertrophied heart following aortic valvulotomy although initially a transient extracellular edema occurs [84] In man no studies are available uncomplicated by disease although it is stated that creatine values increase in early hypertrophy and decrease in extreme hypertrophy [119]

At all events the changes occurring in hypertrophy increase the distances through which oxygen carbon dioxide and other products of metabolism must travel Whether this is compensated for by an increase in volume flow of blood per unit of heart muscle by a further reduction in the percentage saturation of the coronary venous blood or by an increase in the myoglobin content of the myocardium remains to be determined

In the rabbit, aortic valvulotomy,[64] hypertension from removal of buffer nerves,[59] carotid-jugular anastomosis,[3] and cholesterol feeding with marked sclerosis of the coronary arteries [65] are all effective while in the rat induction of renal hypertension,[60] experimental renal insufficiency by partial nephrectomy,[16] increased activity of the heart by thyroid feeding or exercise,[83 155] administration of DCA,[153] all result in considerable hypertrophy. However cholesterol feeding with or without thiouracil, so effective in the dog, does not induce either sclerotic changes in the coronary arteries or heavy hearts in the rat.[4]

In the dog, hypertrophy is not so easily produced and its degree is mild as compared with that in the rat and rabbit. Intracardiac fistula,[67] pulmonary artery constriction in the pup but not in the adult dog [66–68 140] lead to right ventricular hypertrophy, while the combination of treadmill exercise with intravenous injection of lycopodin spores and vanilla bean seeds gives a questionable hypertrophy.[8] Left ventricular hypertrophy in pups, but not in adult dogs, follows aortic stenosis or insufficiency,[37 66 68 147] intracardiac fistulae,[67] but does not occur after arteriovenous fistulae.[65] Although the combined feeding of thiouracil and cholesterol causes large and diffuse coronary artery lesions with a marked decrease in arterial lumen, no evidence of hypertrophy is found.[165]

The varied success in the dog is difficult to evaluate since the cardiac work, metabolism and coronary blood flow, upon the relationship of which hypertrophy is presumed to depend, were not known in these experiments. Actually, the heart weight/body weight ratio in the smaller animals as well as those reached in clinical heart disease are still less than the normal ratio in the dog.[81] This suggests the possibility that the experimental difficulty may arise from the fact that the dog heart is already maximally hypertrophied.

Since significant cardiac hypertrophy has not been created or studied in a suitable experimental animal nor studied in man in situations uncomplicated by disease, its effect on cardiovascular dynamics and the coronary circulation is not known and no definitive statement can be made. However, anatomical studies indicate that such hearts may be under a considerable circulatory handicap. In cases of hypertrophy associated with hypertension, rheumatic fever and arteriosclerosis of the coronary arteries with death from heart failure, the average muscle fiber diameter ranges from 15 μ to 26.5 μ with a mean of 20 μ as compared to a mean of 14 μ for normal heart fibers. The average number of muscle fibers supplied by a capillary is 1.24 or essentially the same as in a normal

systemic blood pressure venous pressure cardiac work or metabolism is not of itself a measure of the ability of a heart to do work for these will vary with the metabolic needs and the stresses to which the heart is exposed However combinations of observations which relate the response of a heart to its load are helpful

Normally the extraction of oxygen from the systemic arterial blood approximates 4 to 6 volumes per cent Provided that the oxygen usage and blood volume are within the normal range a considerable increase in this arteriovenous difference indicates a reduced state of nutrition of the peripheral tissues and suggests heart failure

The demonstrations that the release of energy for a given heart size or load[37] and that the fraction of released energy that is utilized by the heart[14] both decrease in heart failure have been considered as fundamental mechanisms in heart failure However studies do not indicate that the amount of easily available energy is grossly decreased in such hearts and the idea that a gross decline in efficiency of a heart is synonymous with a reduced cardiac capacity for work or heart failure requires experimental validation

A proper measure of the normalcy of a heart is the state of contractility of its ventricles and a considerable change in this is suggestive evidence of heart failure However translation into measurable quantities in experimental animals has been exceedingly difficult because of the lack of adequate methods of study and as a result any statement regarding the state of contractility of a given ventricle on this basis must be viewed with some skepticism In the heart lung preparation and heart *in situ* the discharge of each ventricle during systole varies directly with its size during the preceding diastole irrespective of whether its contained blood flows from the atrium or is residual blood left from the preceding systole Ideally to determine the state of contractility an experimental curve must be established of the relation between cardiac output or better work per beat and diastolic fiber length of each ventricle at different levels of cardiac output The cardiac output can be obtained with considerable accuracy the diastolic fiber length has never been adequately determined experimentally although the size of both ventricles together has been estimated by use of the x ray or a cardiometer In addition determination of diastolic fiber length of both ventricles is always complicated by the inability to separate the portion of the diastolic size due to stretch by its contained blood from that due to the inevitable myocardial edema which appears early in such preparations[10]

It is a reasonable expectation that normally the effective atrial

HEART FAILURE

Heart failure indicates that the activity of a heart is not adequate to supply the peripheral tissues with their needs. Studies on acute heart failure are considerable, but the information gained is not too revealing as to the mechanisms involved or as to the means of determining the time of onset. The general process has been studied as the hearts naturally fail, by the production of localized or generalized coronary insufficiency, by local or generalized myocardial depression and damage. As most acute experiments progress in the open or closed-chest preparation or in the heart lung preparation, the heart generally becomes large and flabby and death from heart failure is generally the characteristic and ultimate finding. With time in the heart-lung preparation if the work is kept constant, the metabolism increases or decreases, the efficiency decreases or shows no change, atrial pressure increases, while for an equivalent work the heart size is increased.[161] In the heart-lung preparation or with the *heart in situ, generalized coronary insufficiency induced by pitressin*,[10, 175] aluminum,[8] or starch granules,[146] which decrease coronary inflow, or generalized myocardial depression and damage induced through chloral hydrate, chloroform, potassium chloride,[38, 57] generally lead to an increase in heart size, augmentation of left and right atrial pressure, arteriovenous oxygen difference, and a decrease in aortic blood pressure, cardiac output, work and efficiency. At times there may be hepatic and pulmonary congestion. Following localized myocardial damage from cautery of the ventricle[160] or local coronary insufficiency through occlusion of a coronary ramus,[91] significant alterations in cardiac output, heart size, efficiency, and atrial pressure are generally not observed, although the latter may be elevated if, prior to coronary occlusion, peripheral muscular exercise is *induced or the blood volume and/or venous return are* augmented. By intravenous administration to dogs of large volumes of blood or albumin solution, cardiac output has been found to plateau in the presence of progressively rising mean systemic venous pressure.[56] By combining hypervolemia with myocardial weakness (quinidine injection) in cat hearts beating *in situ*, disassociation between right and left heart failure has been produced. As these hearts recover, the right heart shows failure as evidenced by an increase in right auricular pressure and right dilation, while the left auricular *pressure decreases and the left ventricle is not dilated*.[141]

Which, if any, of these recordable changes is a reliable and early indicator of failure or weakness of the myocardium remains to be determined. Taken separately, the actual level of cardiac output

upplying each ventricle with blood is a function of its dynamic or *in vivo* volume-elastic (V E) curve and the degree of fulness of the system Dynamic semi V E curves in the exposed dog heart beating *in situ* indicate that the system supplying the left ventricle is either much smaller than the right or is less distensible for the pressure rise in it is greater than in the right ventricle for the same inflow (Fig 73) In either case the atrial venous systems and especially the right, are so highly distensible that a considerable volume of blood can be put into or removed from them without causing a readable change in mean atrial pressure [1,3] To correctly indicate the presence or absence of such a change the pressure in the atrium at point C (Fig 72) must be recorded by an adequate phasic pressure recorder

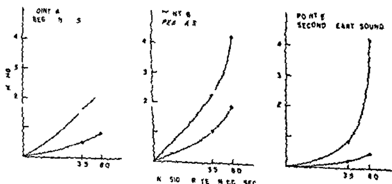


Fig 73 – Semi volume-elastic curves of right and left atriovenous-ventricular cavities at various *points of the* atrial cycle Slightly modified from Opdyke

In addition to the effective atrial pressure at the V point the extent of transfer of blood *from atria to* ventricles for any heartbeat depends on the relative size *of the atrio-*venous reservoir system and its respective ventricular cavity the effective pressure in the atria and ventricles the area *of the opening* between each atrium and ventricle the duration of the time *of filling* of the ventricles and the *in vivo* V E curves of the ventricle as well as of the atrio-venous systems and possibly *active relaxation* of the ventricles The latter possibility has been *invoked* to explain the apparent lack of correspondence of atrial pressure and cardiac output in normal human under widely different *dynamic* states [18] The latter experiments could be better evaluated if the deductions were made from simultaneously recorded phasic *atrial* and intrapleural pressure curves

pressure will vary with the degree of ventricular filling and that the stroke volume or cardiac output will vary only with the degree of ventricular filling. Since diastolic ventricular size is difficult to determine, evidence of the state of contractility of the myocardium might be deduced from a change in the relation of effective atrial pressure to the systolic discharge per beat. With time, in the heart lung preparation an increase in this relationship is a characteristic finding and, as such hearts become weak, this relationship tends to follow that of diastolic size to cardiac output.[19] However quantitation and evaluation of this relationship is difficult when the heart is *in situ* and in a more nearly normal dynamic environment. In such a situation, it has not yet been demonstrated that cardiac output is a primary function of effective atrial pressure, and that a change in this relationship can be used as an index of a failing heart. A change in stroke volume could be produced either by altering the degree of diastolic filling, or by varying the amount of residual blood left in the ventricle at the end of systole or by a combination of

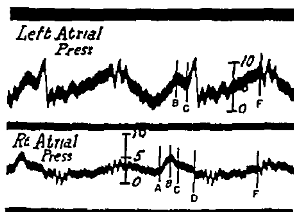


FIG. 72.—Simultaneously recorded left and right atrial pressures in the open-chest dog. Vertical intercepts at A, C, F: beginning of atrial systole, onset of ventricular isometric contraction period, closure of aortic and pulmonary valves respectively. (Opdyke *et al.*[15])

these two factors. Although no good evidence exists to indicate the operation of the latter, its presence would obscure any consistent relationship between effective atrial pressure and cardiac output. The point on the effective atrial pressure curve of most significance *in filling the ventricles is that just before the beginning of ventricular* filling, at which time the atrium and associated veins are closed from the ventricular cavities (Fig. 72). Presumably this point is that of maximal atrial venous volume and of minimal volume of blood contained in the ventricles. The pressure in the atrial venous system

coronary A-V oxygen difference and the coronary flow and oxygen usage per 100 grams of left ventricle per minute were all only slightly increased over normal values.[36]

Although the ultimate effects of anoxia on cardiac tissue are obviously disorganization and death, the steps by which this final disorientation is effected have not been established. Isolated studies have been reported concerning associated biochemical changes. In experimental coronary occlusion or generalized myocardial oxygen deficiency of short duration, in the potentially infarcted area glucose is still slowly absorbed but cardiac glycogen decreases.[41,67] Muscle lactic acid increases with an associated increase in pH and the former is now released into the coronary venous blood rather than absorbed.[114,115] An extracellular edema apparently develops without significant change within the fibers themselves.[35,101] (See, however, experiments of Moore *et al.*[114,11] which indicate that potassium is released into the coronary venous blood, presumably in equilibrium with the potentially infarcted myocardium.)

Finally, on the basis of the consideration in Chapters 5, 6, and 7 of the determinants of coronary flow, cardiac work, and the mechanism of drug action, one can speculate as to the requisite actions of a drug to be of greatest use in heart disease. If one is dealing with *congestive* heart failure arising from hypertension and valvular disease involving increased cardiac work, the drug of choice should be one that increases the vigor of cardiac contraction and increases coronary inflow by decreasing the resistance to coronary flow. Failure can occur when there is a decrease in total energy release in cardiac contraction at a given fiber length (energy failure) or the fraction of total energy output put to work can decrease (efficiency failure). If these mechanisms hold, then a drug should hold a favorable balance between increased vigor of contraction and coronary flow so as to increase efficiency. However, methods and studies of heart failure with the heart *in situ* have not advanced sufficiently far to warrant even speculation as to the drug of choice.

If one is dealing with a coronary insufficiency arising either from a constriction or occlusion of a coronary artery, the drug of choice should be one that decreases pain, decreases the size of the potential infarct by opening up intra- or extracardiac collaterals, decreases the tendency for fibrillation, and increases coronary inflow. Of these desired characteristics only pain has been tested in man. For the remainder recourse of necessity has been in experimental animals. Viewed in this light, the experimental evidence for the favorable action of any particular drug is not impressive and the mechanism of action is not revealed. As already indicated earlier in this chapter

If, then, the state of contractility of the myocardium as measured by atrial pressure and cardiac output or work is to be used as an index of heart failure, it must be done with the realization of the possibility of variations in completeness of emptying of the ventricle, of active changes in relaxation of the ventricles, of active variations in distensibility of the atriovenous bed, each of which alone would alter the relationship of atrial pressure to cardiac output and for the detection of which no valid experimental method exists.

In humans, heart failure is generally chronic, and in addition to the changes in efficiency, atrial pressure, and the ratio of heart size to cardiac output and atrial pressure there occur an increase in blood volume, peripheral edema, pulmonary congestion, preferential reduction in renal blood flow with sodium and electrolyte and water retention.[26, 43, 44, 111, 11, [illegible]] Comparable studies are not available in which the clinical picture of heart failure has been experimentally produced. The most pressing problem in experimental cardiovascular research is to create such a preparation.

Although critical experimental evidence is lacking, it is reasonable to suppose that failure of the coronary circulation is generally responsible for most heart failure. It will be admitted by all that the first prerequisite of a normally functioning heart is an adequate flow of blood through its coronary system. The ability of a heart to increase its blood flow under conditions of stress must depend ultimately on the coronary system. As long as this system can supply an adequate amount of nutrients, oxygen, electrolyte fluids, hormones and enzymes, and can remove the products of metabolism so as to maintain the *status quo*, the heart will continue to function normally, although at times not to the best advantage; but when this system is inadequate, the heart will undergo a downhill course and failure is inevitable. Such inadequacy accounts for the great bulk of cardiac failure. In this group of coronary inadequacies we may put hearts failing with valvular lesions, hypertension, hypertrophy, coronary constriction and occlusion, or all hearts in which there is not primarily a diffuse myocardial damage arising from such entities as rheumatic fever and diphtheria. This type of failure manifests itself in its late stages as so-called congestive heart failure or a hypodynamic heart, or it may appear abruptly as fibrillation without undergoing a recognizable preliminary stage of congestive heart failure.

What the fundamental changes in the coronary circulation are and what they may induce in the myocardium in congestive heart failure are only beginning to be studied in man with the nitrous oxide method. In five patients with congestive heart failure the

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the effect of aminophylline on the size of an experimental myocardial infarct is equivocal, while *theophylline and papaverine reduce it* moderately [113] The mortality following acute coronary occlusion in conscious dogs is decreased by atropine and the xanthines [99] papaverine [103] dihydroergotamine,[103] anesthesia and section of the stellate ganglia [104 107] Finally, in the anesthetized dog with a ligated coronary artery, various drugs (nitrites, theophylline preparations, adenylic acid epinephrine changes in concentration of oxygen and carbon dioxide in the blood do not increase the collateral coronary blood flow directly measured when the perfusion pressure in the non occluded coronary arteries is kept constant [191] All these drugs may act by reducing the degree of vasoconstriction of the *unaffected coronary vessels, thus reducing the possibility of fib*rillation and permitting the collateral bed to develop It should be emphasized that such changes in infarcts were obtained in preparations without sclerosis of the coronary bed and with massive doses of the drug The possibility might be remote that comparable changes would occur in diseased coronary bed

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